

МОЛЕКУЛЯРНАЯ ЭВОЛЮЦИЯ

Molecular Evolution

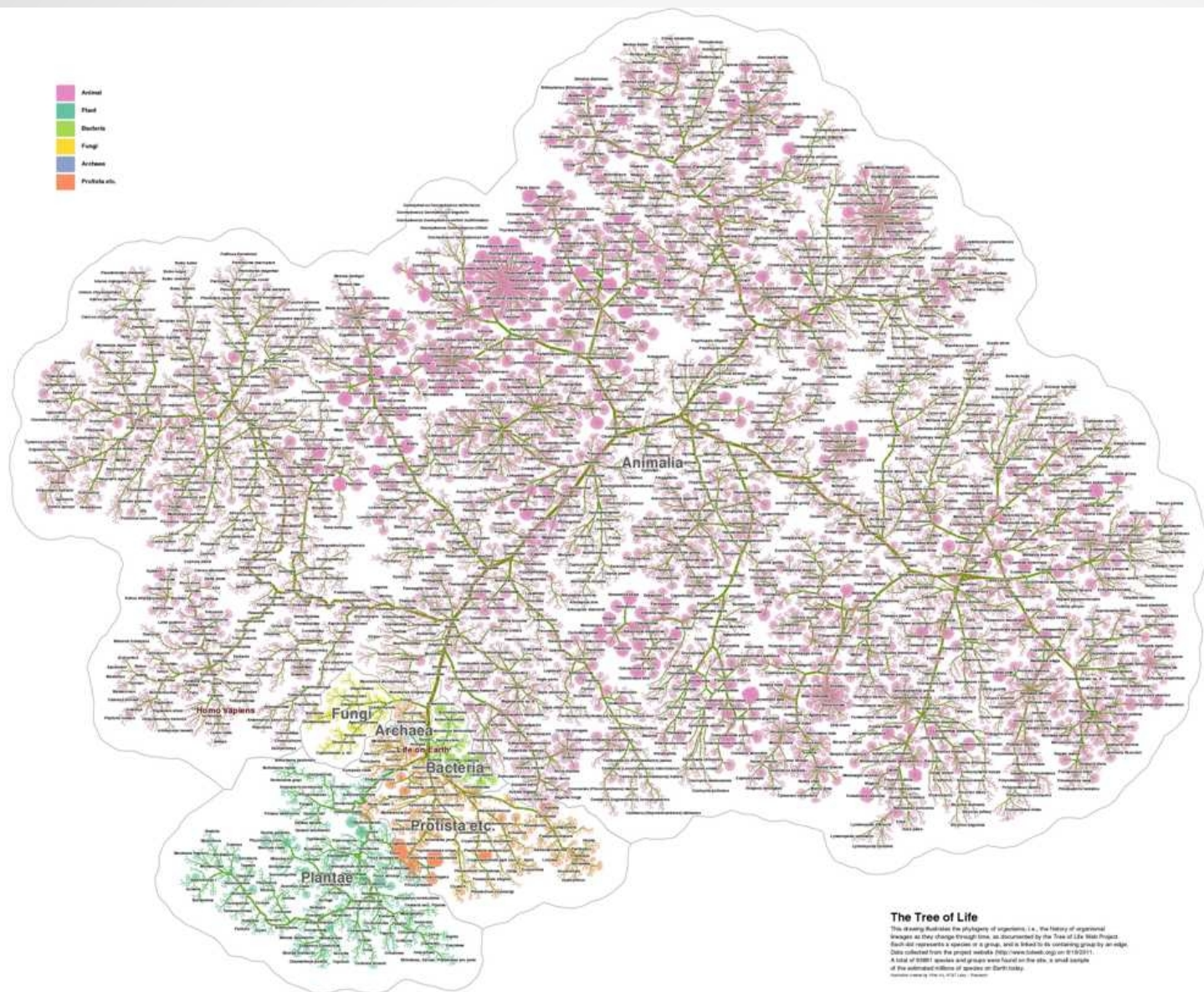
Irkutsk 2016

ОСНОВЫ МОЛЕКУЛЯРНОЙ ЭВОЛЮЦИИ

The Basics of Molecular Evolution.

Irkutsk 2016

Дерево жизни



93891 species

<http://yifanhu.net/TOL/>

МОЛЕКУЛЯРНАЯ ЭВОЛЮЦИЯ

Молекулярная эволюция это процесс изменений в составе последовательностей информационных молекул - ДНК, РНК и белков - в поколениях.

Основные вопросы молекулярной эволюции - скорость и степень влияния нуклеотидных замен, нейтральность эволюции или естественный отбор, генетическая природа сложных признаков, генетические основы видообразования, и др.

Irkutsk 2016

Движущие силы молекулярной эволюции

Мутации

- Точечные мутации
- Дупликации
- Делеции
- Вставки
- Инверсии

Транслокации

Рекомбинации

Конверсия генов

Дрейф генов

Отбор

Irkutsk 2016

Структура и функции генов

Гены белок-кодирующие
РНК кодирующие гены

- рРНК
- тРНК
- мяРНК
- ...

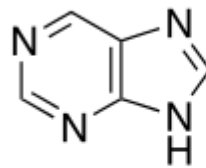
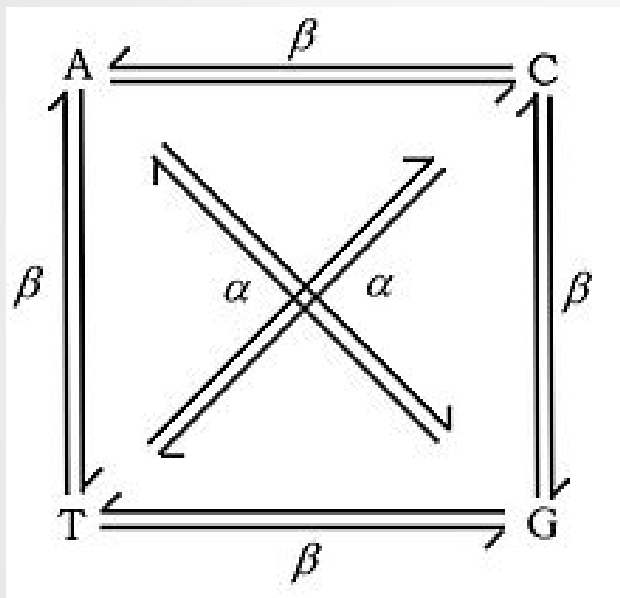
Генетический код

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F	T	TTT	Phe (F)	TCT	Ser (S)	TAT	Tyr (Y)	TGT	Cys (C)
		TTC	Phe (F)	TCC	Ser (S)	TAC		TGC	
		TTA	Leu (L)	TCA	Ser (S)	TAA	STOP	TGA	STOP
		TTG	Leu (L)	TCG	Ser (S)	TAG	STOP	TGG	Trp (W)
S	C	CTT	Leu (L)	CCT	Pro (P)	CAT	His (H)	CGT	Arg (R)
		CTC	Leu (L)	CCC	Pro (P)	CAC	His (H)	CGC	Arg (R)
		CTA	Leu (L)	CCA	Pro (P)	CAA	Gln (Q)	CGA	Arg (R)
		CTG	Leu (L)	CCG	Pro (P)	CAG	Gln (Q)	CGG	Arg (R)
a	A	ATT	Ile (I)	ACT	Thr (T)	AAT	Asn (N)	AGT	Ser (S)
		ATC	Ile (I)	ACC	Thr (T)	AAC	Asn (N)	AGC	Ser (S)
		ATA	Ile (I)	ACA	Thr (T)	AAA	Lys (K)	AGA	Arg (R)
		ATG	Met (M) START	ACG	Thr (T)	AAG	Lys (K)	AGG	Arg (R)
e	G	GTT	Val (V)	GCT	Ala (A)	GAT	Asp (D)	GGT	Gly (G)
		GTC	Val (V)	GCC	Ala (A)	GAC	Asp (D)	GGC	Gly (G)
		GTA	Val (V)	GCA	Ala (A)	GAA	Glu (E)	GGA	Gly (G)
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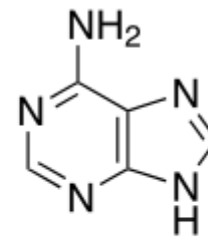
Синонимичные замены

Несинонимичные замены

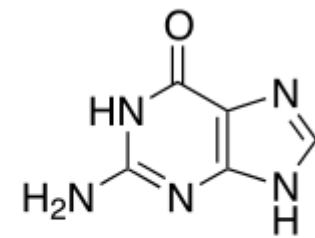
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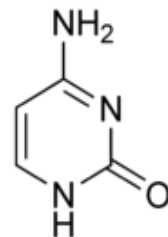
purine
1



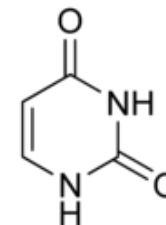
adenine
2



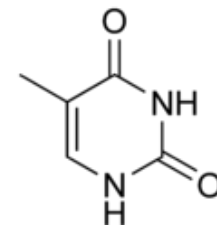
guanine
3



cytosine
4

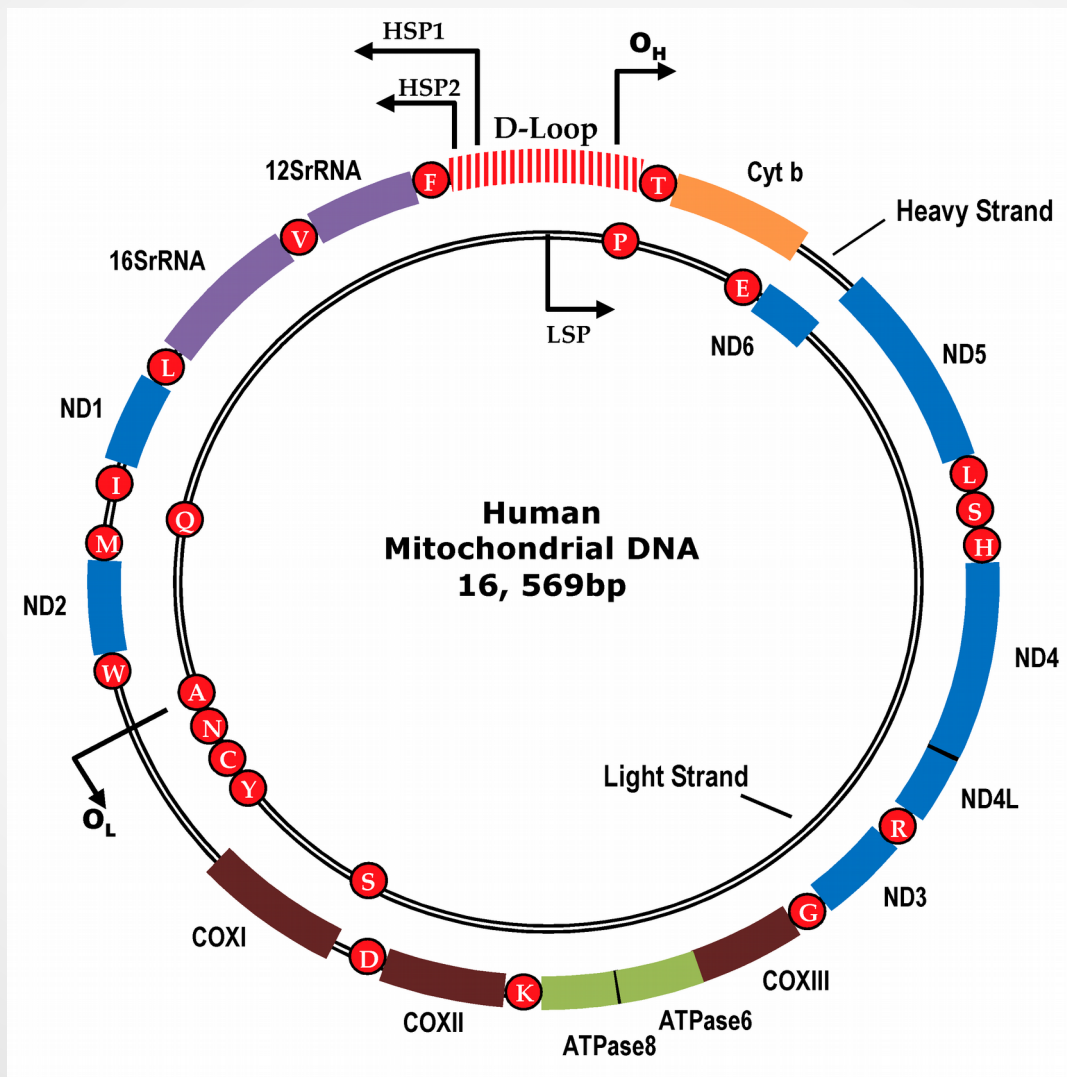


thymine
5



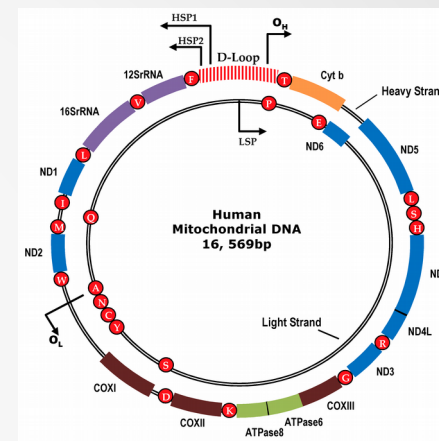
uracil
6

Структура и эволюция митохондриальной ДНК



Структура митохондриальной ДНК

Кольцевая молекула



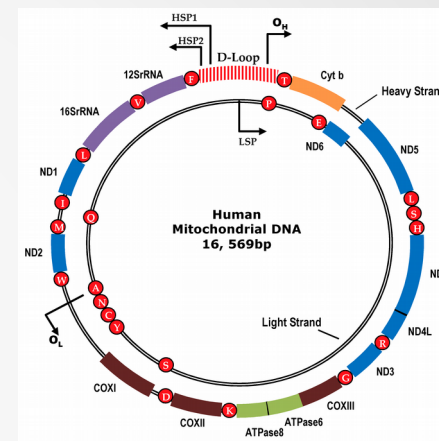
Структура митохондриальной ДНК

В основном, кольцевая молекула

Линейная

У некоторых

- Инфузорий
- Одноклеточных водорослей
- Книдарий



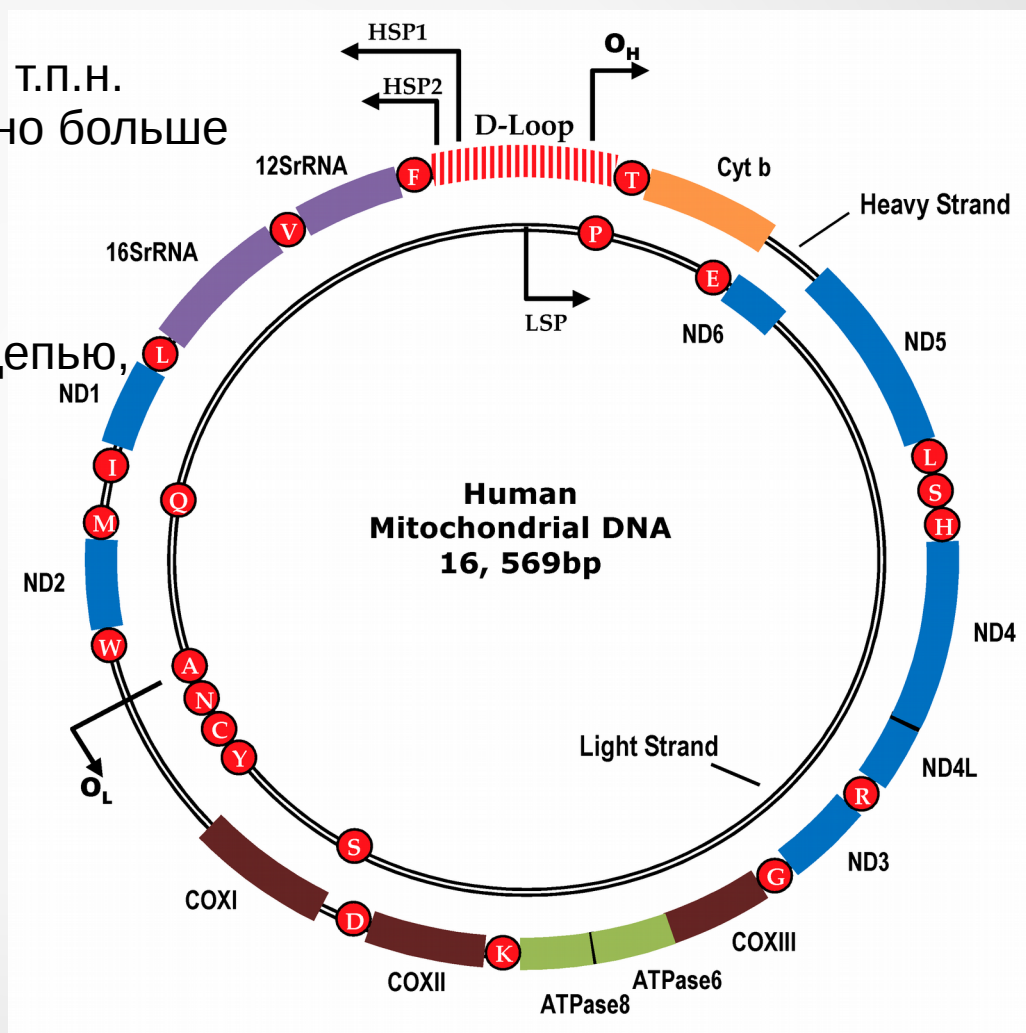
Структура митохондриальной ДНК

Размер

- У большинства животных 16 — 17 т.п.н.
- У растений и грибов — значительно больше

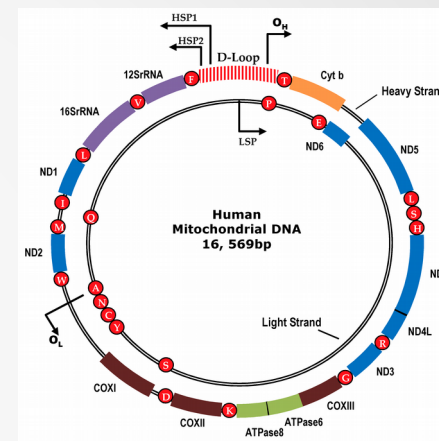
У большинства животных 37 генов

28 генов кодируются легкой (С богатой) цепью,
9 генов — тяжелой (G богатой),
13 гена — кодируют белки,
22 — тРНК
2 — рРНК



Эволюция митохондриальной ДНК

Наследуется по материнской линии



Эволюция митохондриальной ДНК

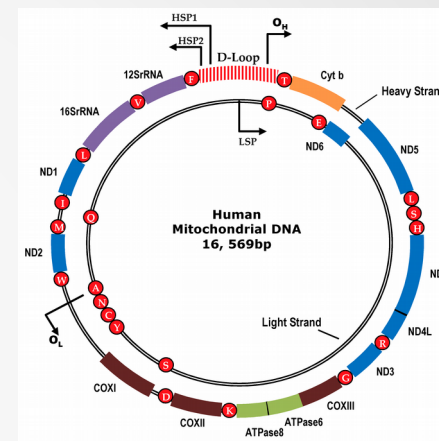
В основном, наследуется по материнской линии

Мужское наследование отмечено для

некоторых

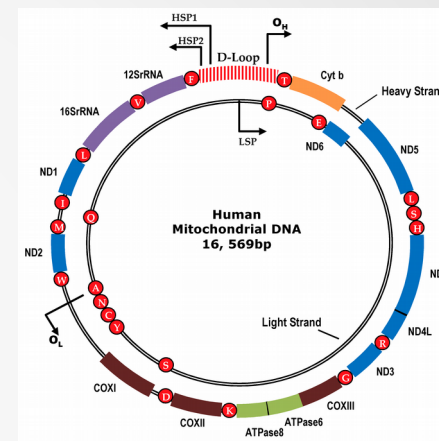
- Моллюсков
- Насекомых

Единичные случаи отмечены мышей, домашних кур и человека



Эволюция митохондриальной ДНК

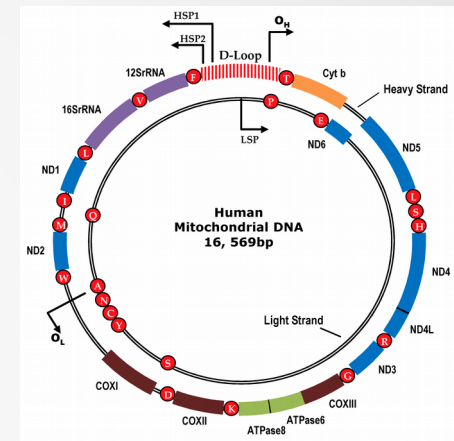
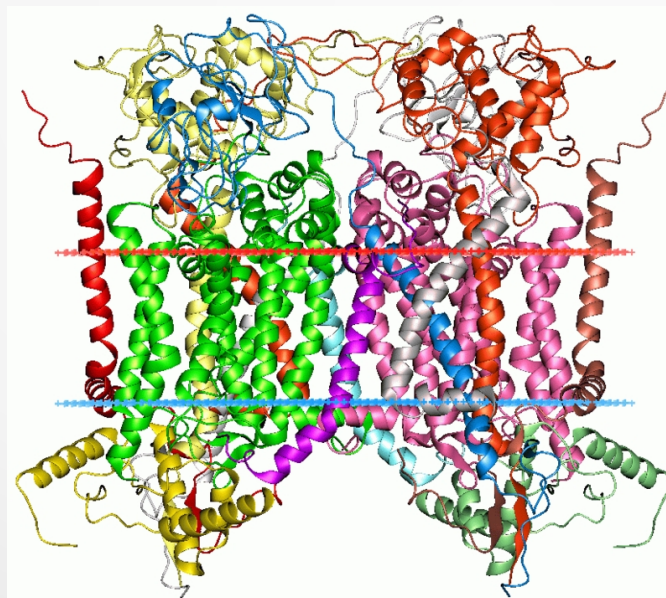
Скорость эволюции, в среднем, на порядок выше, чем в ядерном геноме.



Эволюция митохондриальной ДНК

Вопросы

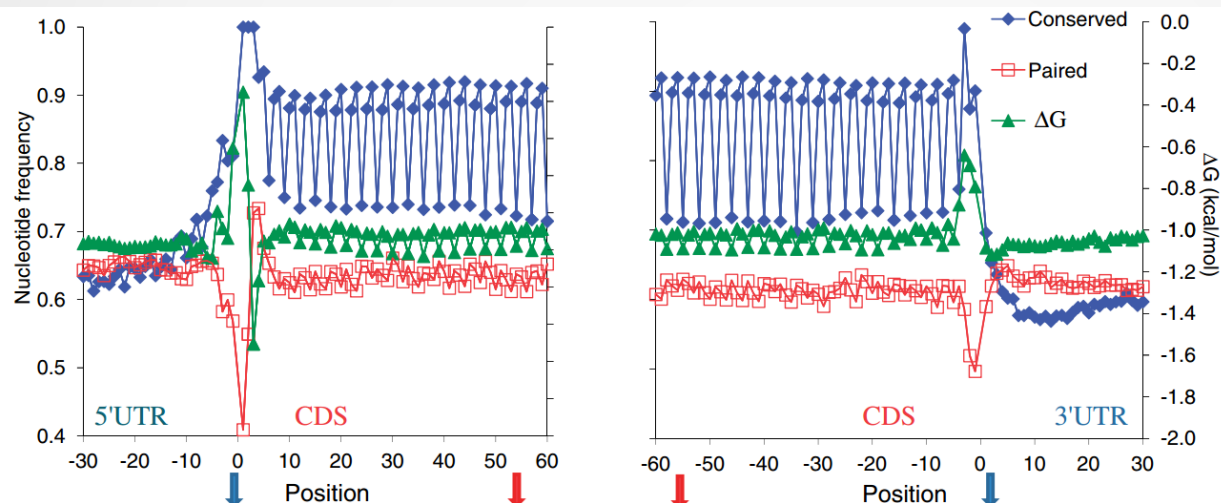
Ко-эволюция с ядерным геномом



Эволюция митохондриальной ДНК

Вопросы

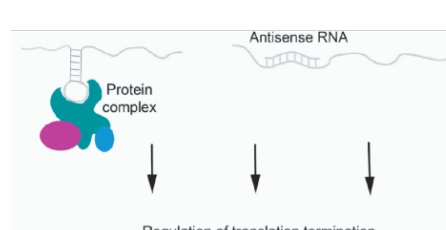
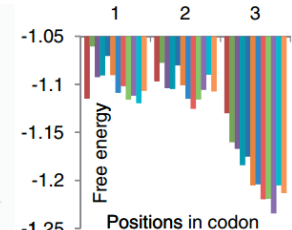
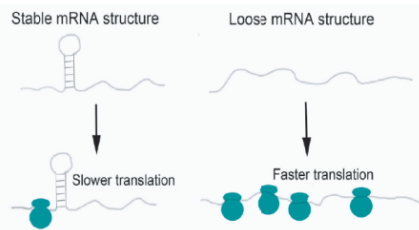
Роль синонимичных замен



In the vicinity of the start codon
Translational control

Coding region – Periodicity
Translation frame monitoring

In the vicinity of the stop codon
Subcellular localization and stability

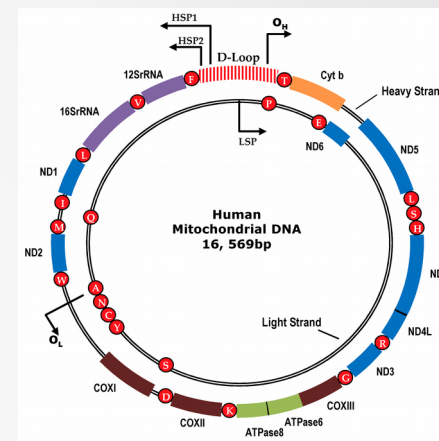


Protein abundance

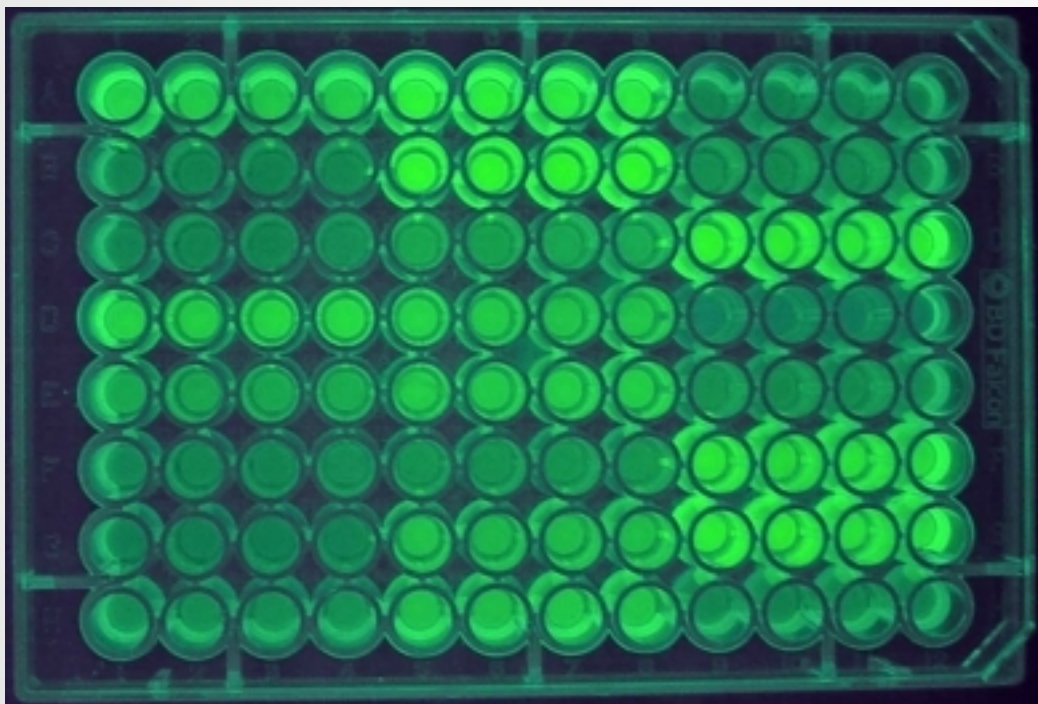
Protein degradation

mRNA decay

Posttranslational regulation



Эволюция митохондриальной ДНК



Kudla G, Murray AW, Tollervey D, Plotkin JB. Science. 2009;324:255–258.

REPORTS

Coding-Sequence Determinants of Gene Expression in *Escherichia coli*

Gregory Kudla,¹ Andrew W. Murray,² David Tollervey,³ Joshua B. Plotkin¹

Synonymous mutations do not alter the encoded protein, but they can influence gene expression. To investigate how, we engineered a synthetic library of 154 genes that varied randomly at synonymous sites, but all encoded the same green fluorescent protein (GFP). When expressed in *Escherichia coli*, GFP protein levels varied 250-fold across the library. GFP messenger RNA (mRNA) levels, mRNA degradation patterns, and bacterial growth rates also varied, but codon bias did not correlate with gene expression. Rather, the stability of mRNA binding near the ribosomal binding site explained more than half the variation in protein levels. In our analysis, mRNA binding and associated rates of translation initiation play a predominant role in shaping expression levels of individual genes, whereas codon bias influences global translation efficiency and cellular fitness.

The library of codon bias positions that preferentially codon correlate with the abundance of leucopyran (62As (1, 2) and thereby increase translational efficiency (3) and accuracy (4). Recent experiments have revealed other effects of silent mutations (5-7). We combined a library of genes fluorescent protein (GFP) genes that varied randomly in their codon usage, but encoded the same amino acid sequence (8). By placing these constructs in identical regulatory contexts and measuring their expression, we isolated the effects of synonymous variation on gene expression.

The GFP gene consists of 240 codons. For 226 of these codons, we introduced random silent mutations in the third base position, while keeping the first and second positions constant (Fig. 1A). The resulting synthetic GFP constructs differed by up to 140 silent substitutions, with an average of 134 substitutions between pairs of constructs (Fig. 1B and figs. S1 and S2). The range of third-position GC content (GC%) across the library of constructs encompassed virtually all (99%) of the GC% values among endogenous *Escherichia coli* genes, and the variation in the codon adaptation index (CAI) (9) contained most (96%) of the CAI values of *E. coli* genes (Fig. 1C).

We expressed the GFP genes in *E. coli* using a T7 promoter vector, and we quantified expression by spectrofluorometry. Fluorescence levels varied 250-fold across the library, and they were highly reproducible for each GFP construct (Spearman $r = 0.98$ between biological replicates) (Fig. 3). Fluorescence variation was consistent across a broad range of experimental conditions (Fig. 3D).

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17. We thank A. Ewington of Harvard University and L. Sachs and K. Bauer of Brown University for providing the mammalian and rat cell lines. This work was funded in part by NSF grant 0732147 (J.B.P.) and NSF grant 0645931 (Division of Information and Intelligent Systems) (G.P.).

Supporting Online Material
www.sciencemag.org/content/324/5851/255/DC1
SOM Text
Figs. S1 to S3
SOM Movie

References

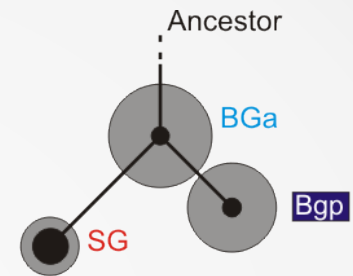
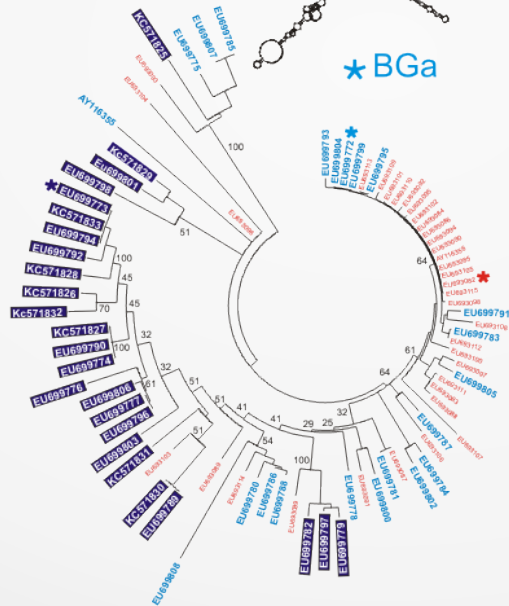
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www.sciencemag.org SCIENCE VOL 324 10 APRIL 2009 255

Baikal Oilfishes Cytb



Big Baikal oilfish,
BGa and BGP



- The frequencies of the main haplotypes
- The nucleotide diversity



Little Baikal oilfish, SG

Эволюция митохондриальной ДНК

Вопросы остались

REPORTS

Population Size Does Not Influence Mitochondrial Genetic Diversity in Animals

Eric Bazin, Sylvain Glémin, Nicolas Galtier*

Within-species genetic diversity is thought to reflect population size, history, ecology, and ability to adapt. Using a comprehensive collection of polymorphism data sets covering ~3000 animal species, we show that the widely used mitochondrial DNA (mtDNA) marker does not reflect species abundance or ecology: mtDNA diversity is not higher in invertebrates than in vertebrates, in marine than in terrestrial species, or in small than in large organisms. Nuclear loci, in contrast, fit these intuitive expectations. The unexpected mitochondrial diversity distribution is explained by recurrent adaptive evolution, challenging the neutral theory of molecular evolution and questioning the relevance of mtDNA in biodiversity and conservation studies.

Genetic diversity is a central concept of evolutionary biology that has been linked to organismal complexity (1), ecosystem recovery (2), and species ability to respond to environmental changes (3). A lack of diversity is typically considered an evidence for a small or declining, potentially endangered population (4, 5). Population genetics theory tells us that, for a neutral locus, the expected polymorphism at mutator-drift equilibrium is proportional to the effective population size, the equivalent number of breeders in an ideal, panmictic population. Other factors can of course affect the genetic polymorphism, including population structure (6), population bottlenecks (7), and natural selection (either directly or through genetic linkage (7, 8)), life cycle (9), and mating systems (10). These multiple influences complicate any attempt to interpret the genetic diversity of one particular species in terms of population size (11). Population size, however, presumably varies by several orders of magnitude between species and taxa, so that one would typically predict that abundant species should be, on average, more polymorphic than scarce ones despite the noise introduced by other evolutionary forces.

Meta-analyses of allozyme polymorphism studies were mostly consistent with this theoretical prediction (12, 13). In particular, invertebrate animals were found to be more polymorphic, on average, than vertebrates (13). It was noted, however, that the expected proportional relationship between diversity and effective population size was rarely met (14). DNA-based markers have now replaced allozymes in population genetics studies. Among these, the supposedly nonrecombining and evolutionarily neutral mitochondrial DNA (mtDNA) has been the most widely used marker

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Fig. 1. Average allozymic, nuclear DNA, and mtDNA diversity in eight animal taxa. α is the average allozyme heterozygosity, γ is the average nuclear DNA average synonymous diversity (Kendall test: $\tau = 0.87$, $P < 0.05$); squares, mtDNA average synonymous diversity (Kendall test: $\tau = -0.14$, not significant). Mar, Mammalia (allozymes: 184 species; nuclear: 30 species; mtDNA: 350 species); S, Saurropsida (reptiles and birds: 116, 20, 378); A, Amphibia (61, 4, 56); F, Pisces (bony fish and cartilaginous fish: 183, 22, 270); I, Insecta (156, 73, 511); C, Crustacea (122, 2, 78); E, Echinodermata (sea stars and urchins: 15, 14, 47); and M, Mollusca (46, 9, 125). The near-linear averages of the little-represented Amphibia (four species) and Crustacea (two species) are shown but were not used for the statistical test.

PROCEEDINGS
THE ROYAL SOCIETY

FirstCite
publishing

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Published online

Climate shaped the worldwide distribution of human mitochondrial DNA sequence variation

François Balloux¹*, Lori-Jayne Lawson Handley², Thibaut Jobart¹, Hua Liu³ and Andrea Manica^{1,4}

¹Department of Infectious Disease Epidemiology, Imperial College Faculty of Medicine, MRC Centre for Outbreak Analysis and Modelling, St Mary's Campus, Norfolk Place, London W2 1PG, UK; ²Department of Biological Sciences, University of Hull, Cottingham Road, Hull HU6 7RX, UK; ³Department of Genetics, and ⁴Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, UK

There is an ongoing discussion in the literature on whether human mitochondrial DNA (mtDNA) evolves neutrally. There have been previous claims for natural selection on human mtDNA based on an excess of non-synonymous mutations and higher evolutionary persistence of specific mitochondrial mutations in Arctic populations. However, these findings were not supported by the reanalysis of larger datasets. Using a geographical framework, we perform the first direct test of the relative extent to which climate and past demography have shaped the current spatial distribution of mtDNA sequences worldwide. We show that populations living in colder environments have lower mitochondrial diversity and that the genetic differentiation between pairs of populations correlates with difference in temperature. These associations were unique to mtDNA; we could not find a similar pattern in any other genetic marker. We were able to identify two correlated non-synonymous point mutations in the ND1 and ATP8 genes characterized by a clear association with temperature, which appear to be plausible targets of natural selection producing the association with climate. The same mutations have been previously shown to be associated with variation in mitochondrial pH and calcium dynamics. Our results indicate that natural selection mediated by climate has contributed to shape the current distribution of mtDNA sequences in humans.

Keywords: mtDNA, selection, climate, temperature, human evolution, single nucleotide polymorphisms

1. INTRODUCTION

Mitochondrial DNA (mtDNA) remains by far the most widely used genetic marker in studies of human populations. One assumption behind inferences on past human demographic history is the selective neutrality of the genetic markers employed. There have been claims for natural selection affecting mtDNA, with temperature being highlighted as a possible selective force in a variety of taxa (Ballard & Whitlock 2004) including humans (Torroni et al. 2001; Mishmar et al. 2003; Ruiz-Pesini et al. 2004). However, this has been rejected by several studies, which concluded that human mtDNA sequence variation has not been significantly shaped by climate (Elson et al. 2004; Kivild et al. 2006; Amo & Brand 2007; Ingman & Gyllenstein 2007; Sun et al. 2007). The tests so far have mainly relied on ratios of synonymous and non-synonymous mutations (dN/dS ratio) and to a lesser extent on the evolutionary persistence of mutations in the mitochondrial phylogenetic tree. Interestingly, it has since been shown that dN/dS ratios are largely inadequate when testing for natural selection

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Allozyme heterozygosity (H)

Allozyme heterozygosity (H)

with populations (Kryzhanimsky & Plotkin 2008). Here we take a radically different approach by directly modelling the distribution of worldwide mitochondrial sequence diversity with geography and climatic variables. The most likely origin of anatomically modern humans lies in sub-Saharan Africa, where the most ancient remains (dated to approximately 200,000 years) have been found (McDonnell et al. 2005). It is generally accepted that the human population started expanding in range 50,000–70,000 years ago and then colonized the entire globe with little or no interbreeding with previously established archaic human species (Stringer & Andrews 1988; Macaulay et al. 2005; Liu et al. 2006; Fagundes et al. 2007; Hellenthal et al. 2005; Doshpanov et al. 2009). A signature of this expansion can be seen in the smooth clinal geographical distribution of autologous polymorphisms (Handley et al. 2007). Genetic differentiation between populations increases essentially linearly with geographical distance along landmasses (Relethford 2004; Manica et al. 2005; Ramachandran et al. 2005; Romero et al. 2008) and geographical distance from sub-Saharan Africa is an excellent predictor of the genetic diversity of individual populations throughout the world (Prugnolle et al. 2005a). We can capitalize on these exceptionally strong correlations between genetic

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population size,
and its significance warrants
further testing with other groups and more
detailed analyses.
In animal groups with large populations,
e.g., invertebrates, selective sweeps can frequently reduce mtDNA diversity such that the species' standing variation primarily reflects the time since its last 'genetic drift' (1). However, many animal groups of broad interest to both the scientific community and the general public are those with known or expected smaller populations, for example, humans, endangered species, and 'charismatic' animals. It is in such groups that we predict mtDNA will remain a valuable genetic marker for the study of population history and demography.

1390a

TECHNICAL COMMENT

Comment on "Population Size Does Not Influence Mitochondrial Genetic Diversity in Animals"

Connie K. Mulligan,^{1*} Andrew Kitchen,² Michael M. Miyamoto³

Bazin et al. (Reports, 28 April 2006, p. 570) found no relationship between mitochondrial DNA (mtDNA) diversity and population size when comparing across large groups of animals. We show empirically that species with smaller populations, as represented by eutherian mammals, exhibit a positive correlation between mtDNA and allozyme variation, suggesting that mtDNA diversity may correlate with population size in these animals.

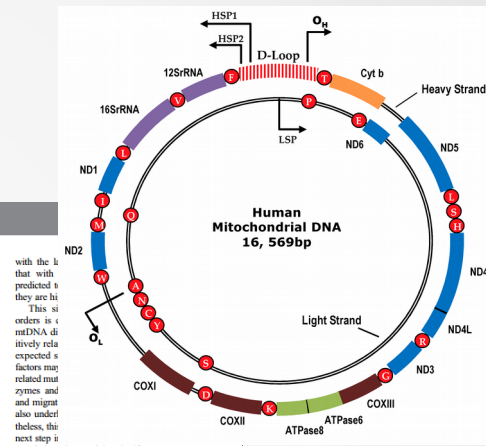
Bazin et al. (1) did not find a positive relationship between mitochondrial DNA (mtDNA) diversity and population size as predicted from population genetics theory for animal groups with larger versus smaller populations, e.g., invertebrates versus vertebrates. In contrast, this relationship holds for nuclear DNA and allozyme markers. The authors propose that the expected relationship is not found for mtDNA because recurrent selective sweeps have reduced mtDNA diversity and thereby homogenized mitochondrial variation across animal groups. In an accompanying article, Eyre-Walker (2) noted that humans are an exception to this mtDNA pattern because of their smaller population size. Specifically, he cites the many studies of human mtDNA, autosomes, and Y chromosomes that have converged on a final estimate of ~10,000 individuals (males and females) (summarized in (3)). Various studies of the X chromosome have also led to a similar estimate of ~10,000 (4, 5), further corroborating the utility of mtDNA for population size estimation in humans. In species with smaller populations, selective sweeps are less likely to occur because fewer beneficial mutations arise and selection is less efficient. Therefore, in species like humans, selective sweeps become less of a concern when estimating population size from mtDNA.

As an initial test of this hypothesis, we extended Bazin et al.'s analysis with a focus on the 47 species of eutherian (placental) mammals in their mtDNA data set for which allozyme heterozygosity (H) were also available (6). We focused on eutherian mammals because of their expected smaller population sizes as well as their greater representation in both databases and closer phylogenetic ties to humans. We edited the alignments for misplaced gaps calculated both synonymous and total mtDNA diversities for coding sequences (π_s and π_t), and then plotted mean π_s and π_t against average H for each order (Fig. 1). A significant positive correlation was found between both π_s and π_t versus H (Kendall test, $\tau = 0.86$ and 0.84 , $P < 0.005$ for each comparison). Thus, we find a positive correlation between mtDNA diversity and allozyme heterozygosity, suggesting that the former correlates with population size as does the latter (1). Interestingly, the order with the greatest mtDNA and allozyme variability (Rodentia) is the one

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and its significance warrants
further testing with other groups and more
detailed analyses.
In animal groups with large populations,
e.g., invertebrates, selective sweeps can frequently reduce mtDNA diversity such that the species' standing variation primarily reflects the time since its last 'genetic drift' (1). However, many animal groups of broad interest to both the scientific community and the general public are those with known or expected smaller populations, for example, humans, endangered species, and 'charismatic' animals. It is in such groups that we predict mtDNA will remain a valuable genetic marker for the study of population history and demography.

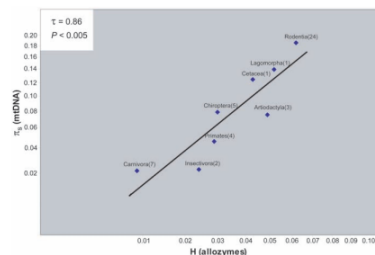
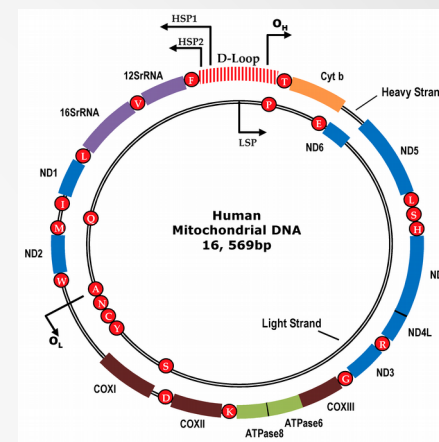


Fig. 1. Arcsine square root plot of mean π_s versus H for eight orders of eutherian mammals (numbers of species are given in parentheses). A nearly identical relationship exists for mean π_t versus H ($\tau = 0.84$, $P < 0.005$). Furthermore, our results are robust in that P remains < 0.005 when three pairs of orders with nearly identical π or H diversities, i.e., Artiodactyla/Chiroptera, Carnivora/Insectivora, and Chiroptera/Primates are counted as ties in the Kendall tests. Individual π_s and π_t estimates for each species were based on the Nei-Gajdosi method with a Jukes-Cantor correction and on the Kimura two-parameter distance with a gamma distribution ($\Gamma = 0.5$), respectively (7). Otherwise, our methods followed those of Bazin et al. (2).

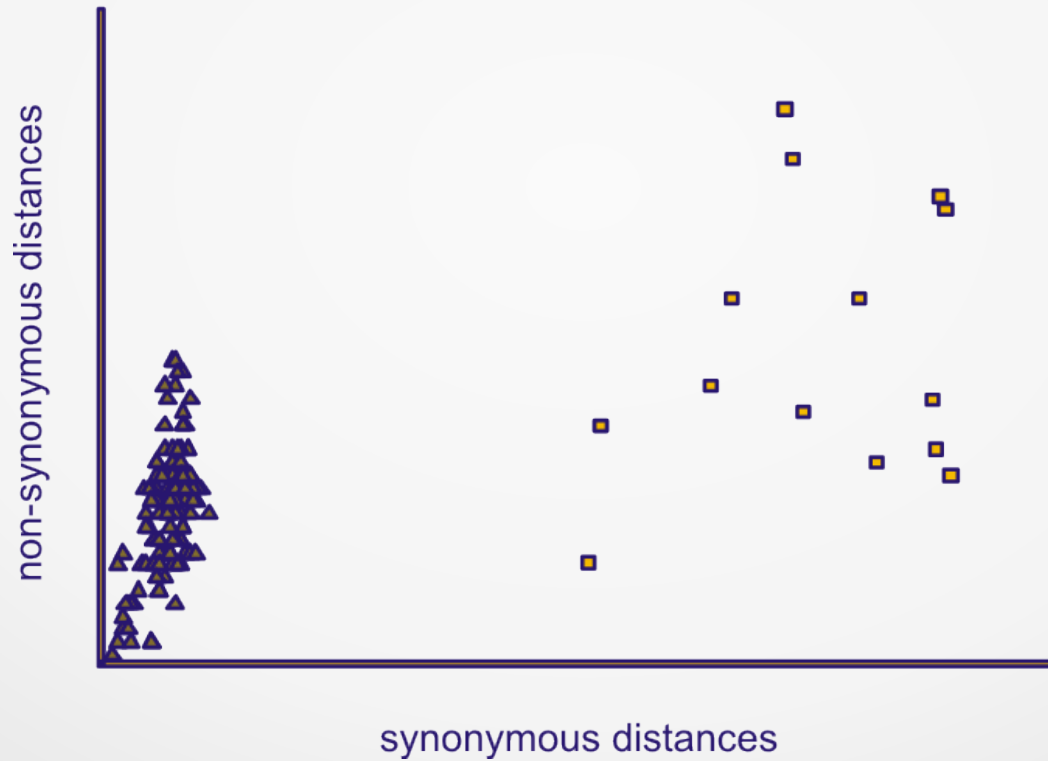
Эволюция митохондриальной ДНК

Спасибо за внимание!



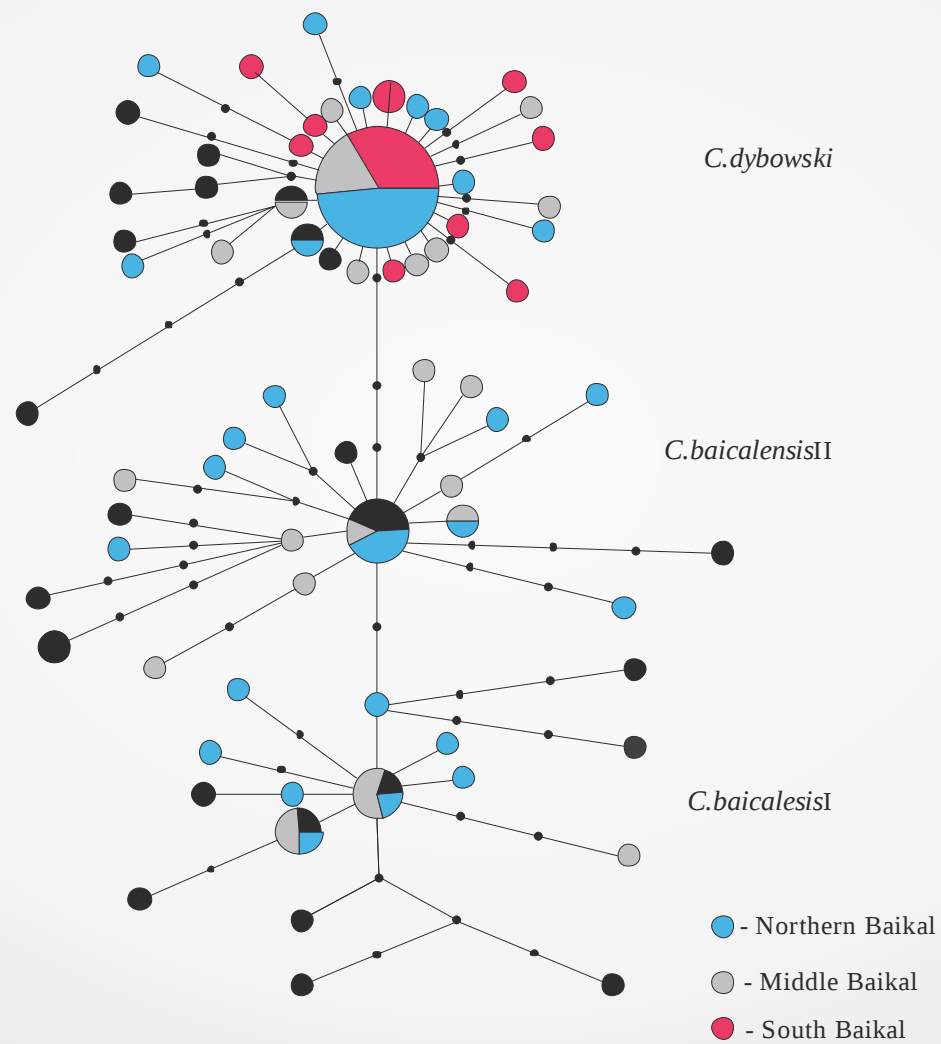
Synonymous vs. Non-synonymous substitutions.

Pairwise species comparisons: non-Baikalian vs. Baikalian

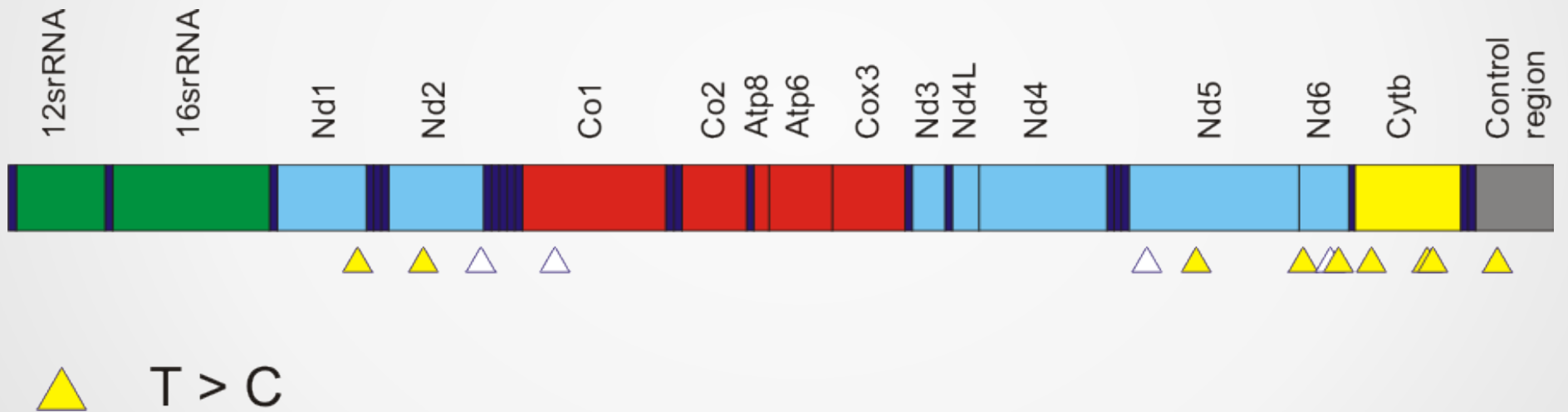


Байкальские голомянки

Baikal oilfishes



Baikal Oilfishes mitochondrial genome



Thank you!



Байкальские голомянки Baikal oilfishes

Большая голомянка (*Comephorus baicalensis* Pallas, 1776)
Big Baikal oilfish

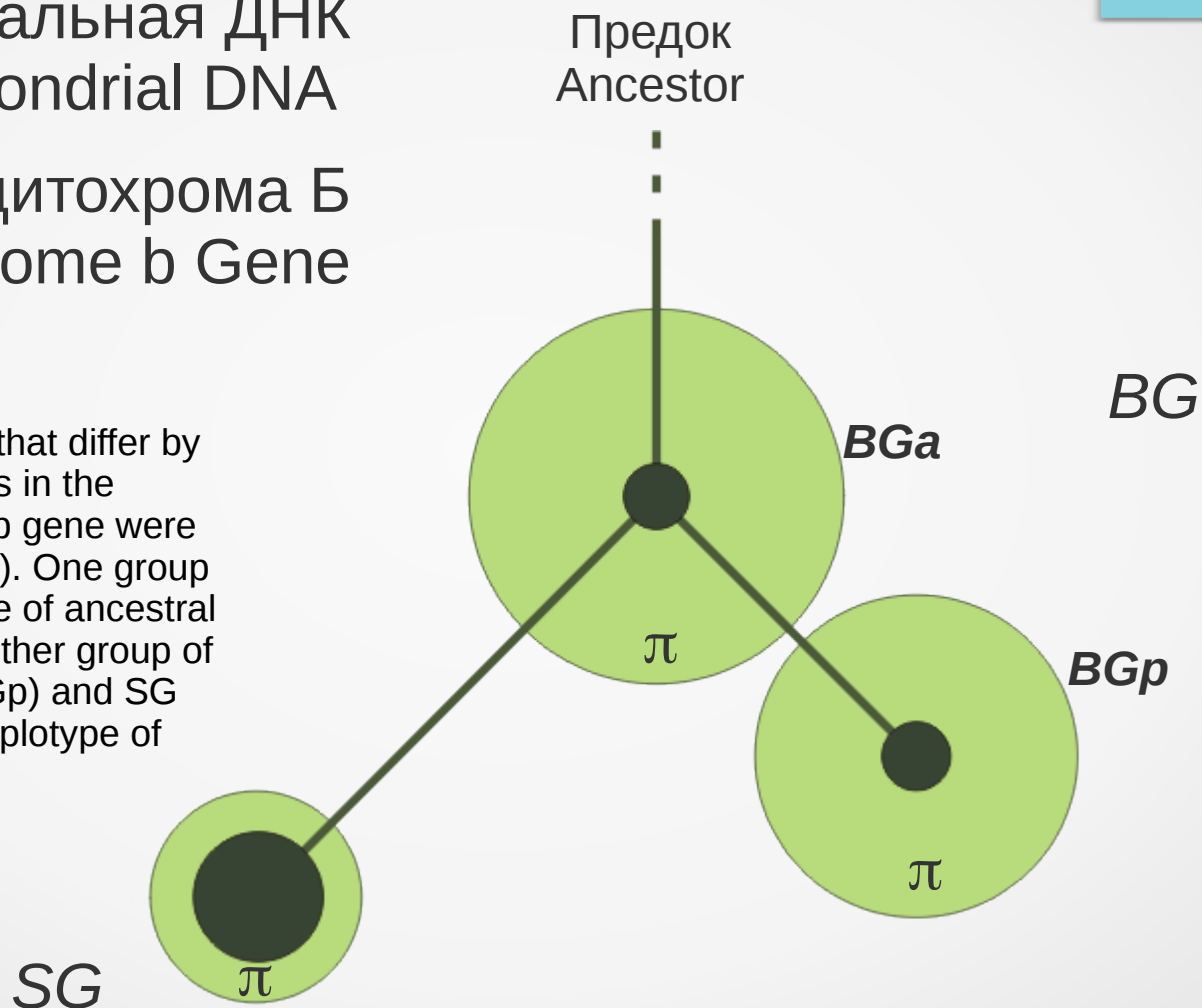
Малая голомянка (*Comephorus dybowski* Korotneff, 1905).
Little Baikal oilfish

Внутри и межвидовые генетические взаимоотношения Within and Between Species Genetic Variation

Митохондриальная ДНК
Mitochondrial DNA

Ген цитохрома Б
Cytochrome b Gene

Two genetic groups of BG that differ by two nucleotide substitutions in the mitochondrial cytochrome b gene were found (Teterina et al., 2010). One group was represented by the line of ancestral haplotypes (BGa), and another group of BG (BG-paraphyletic or BGp) and SG derived from the central haplotype of BGa.



- - Circle diameters are proportional to the frequencies of the main haplotypes.
- - Circle diameters are proportional to the respective values of nucleotide diversity (π).

Численность представителей групп BGa и BGp
The number of representatives of groups BGa and BGp

Анализ
однонуклеотидного
полиморфизма
SNP analysis

$$BGa/BGp = 50/50$$

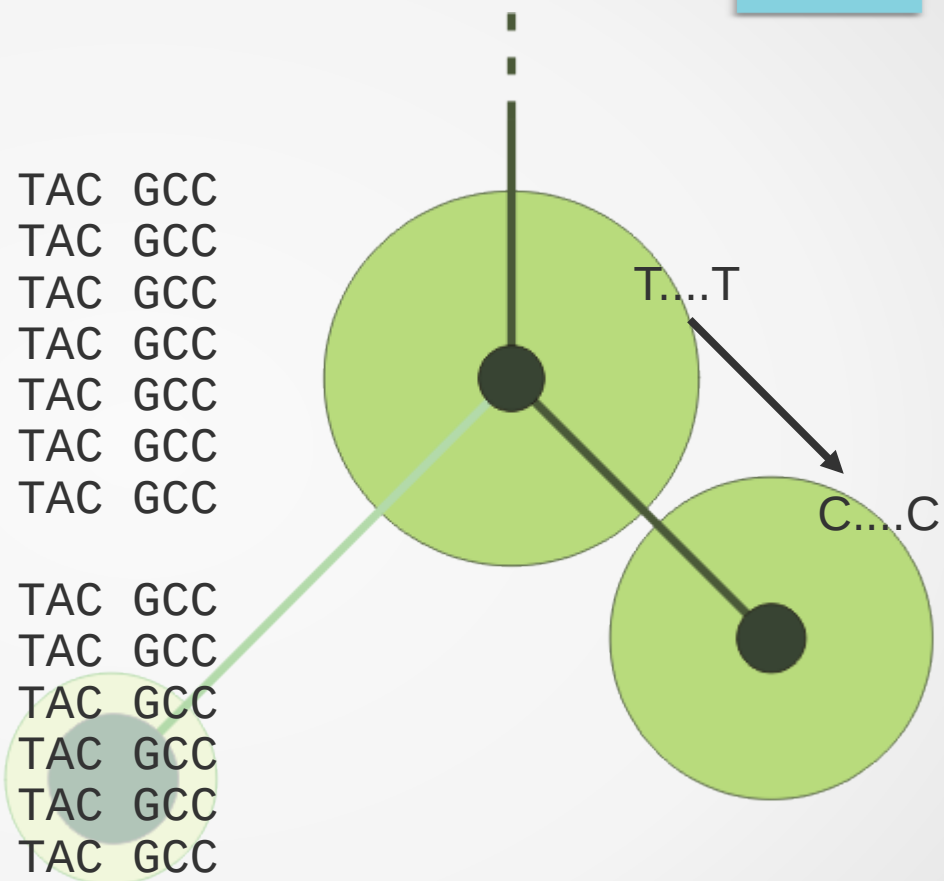
В любом месте, в любое время, в любом возрасте
In any place, at any time, at any age

Замены между основными гаплотипами BGa и BGp

Substitutions between the main haplotypes of BGa and BGp

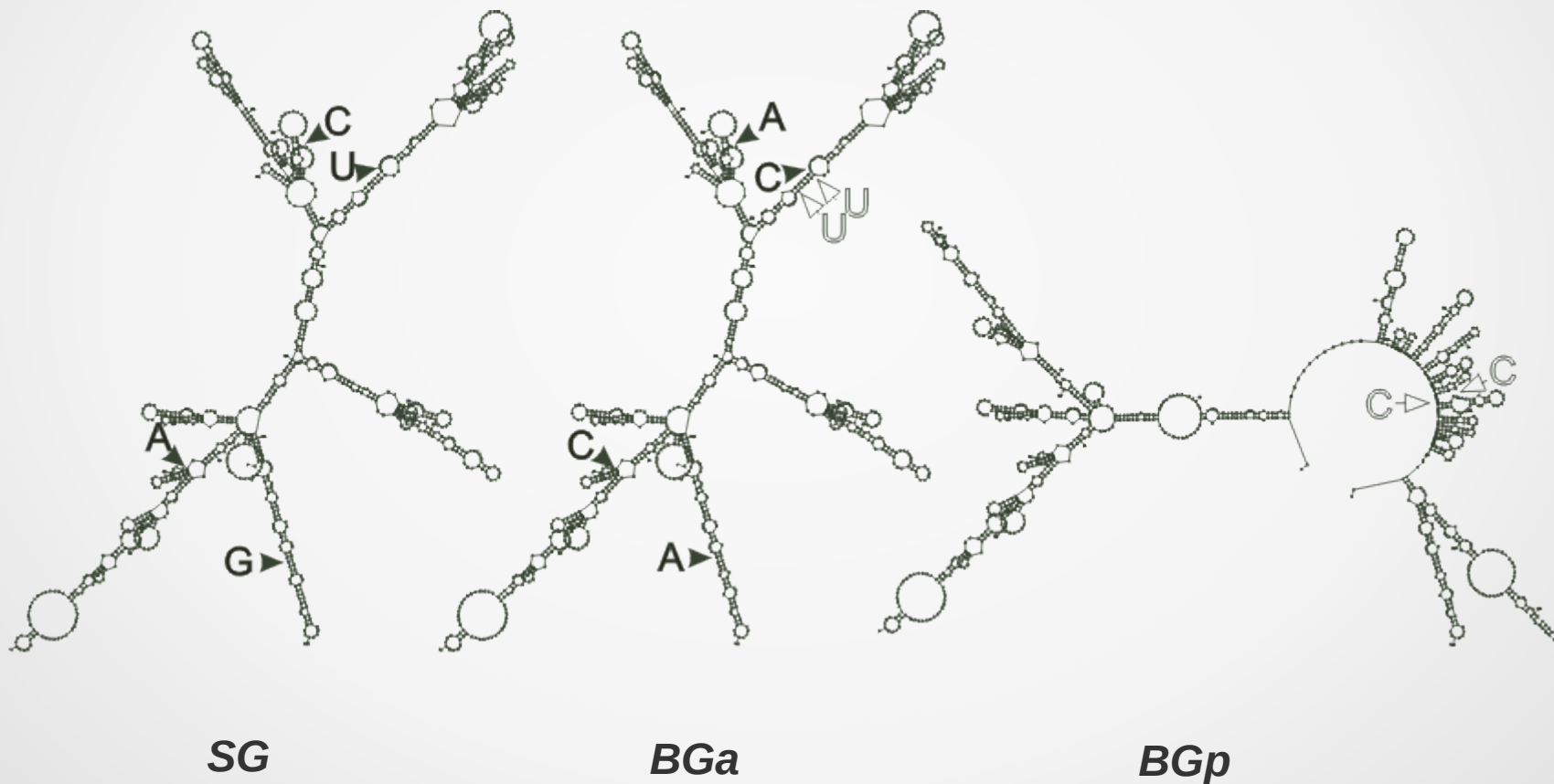
TGG TAC TTC **TTG** TTT GCC TAC GCC
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 TGG TAC TTC **CTG** TTC GCC TAC GCC



Моделирование вторичной структуры мРНК The mRNA secondary structure prediction

Основные гаплотипы
The main haplotypes

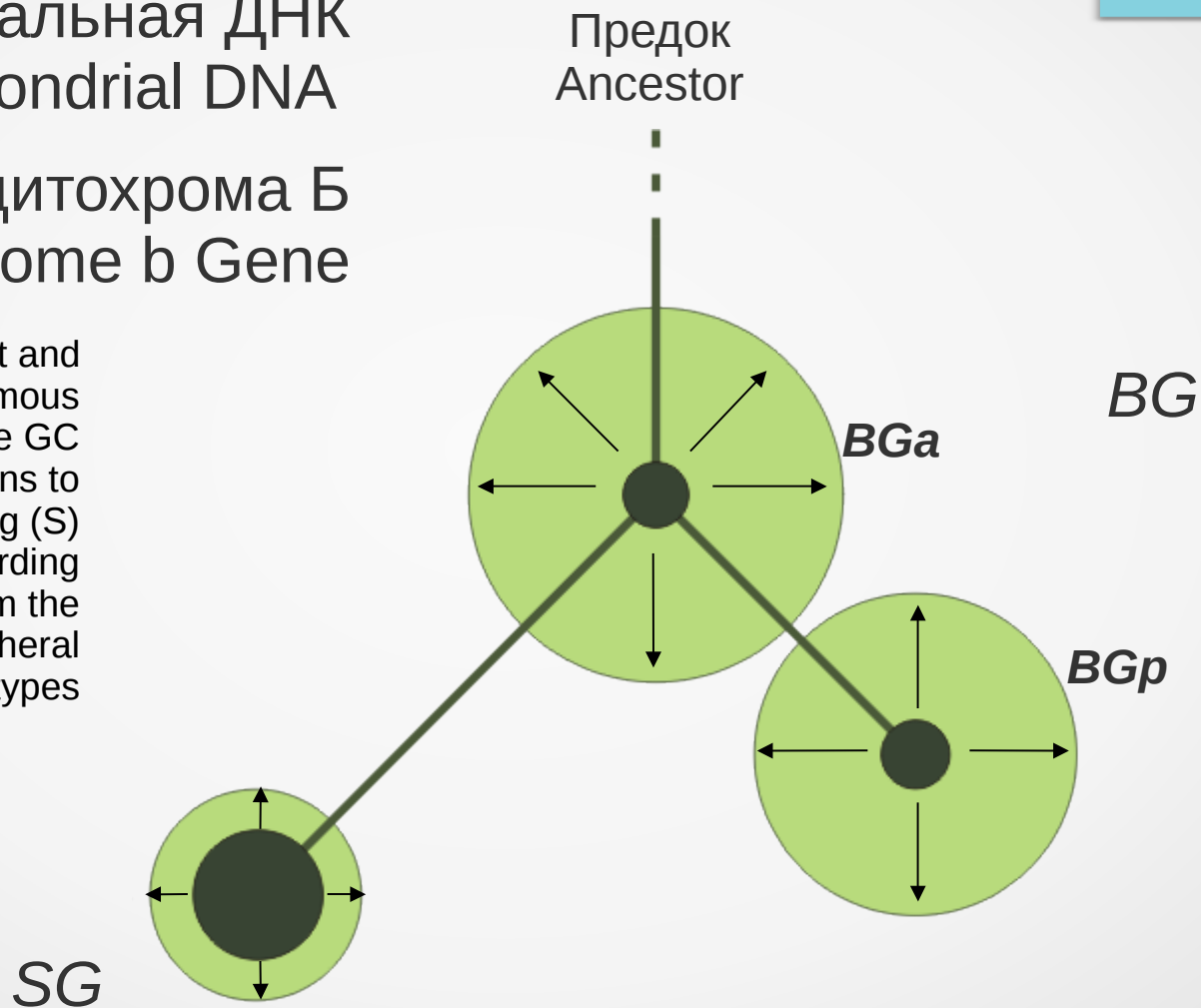


Тест центробежного отклонения замен нуклеотидов Test of Centrifugal Substitution Bias

Митохондриальная ДНК
Mitochondrial DNA

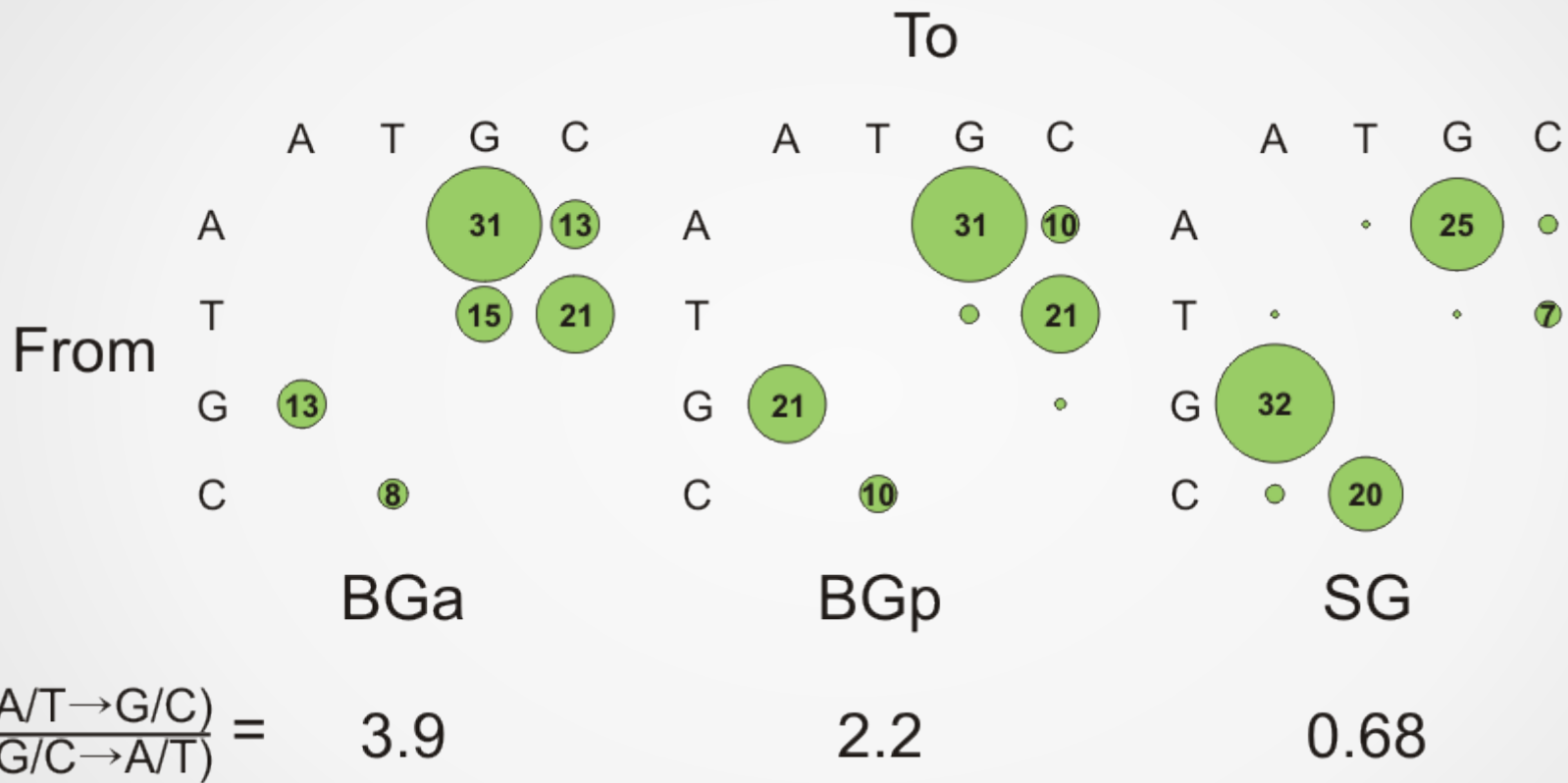
Ген цитохрома Б
Cytchrome b Gene

We analysed the amount and distribution of synonymous mutations, affecting the GC composition (mutations to weak (W) - A,T or to strong (S) - G,C nucleotides), according to their directions from the central to peripheral haplotypes



Тест центробежного отклонения замен нуклеотидов

Test of Centrifugal Substitution Bias



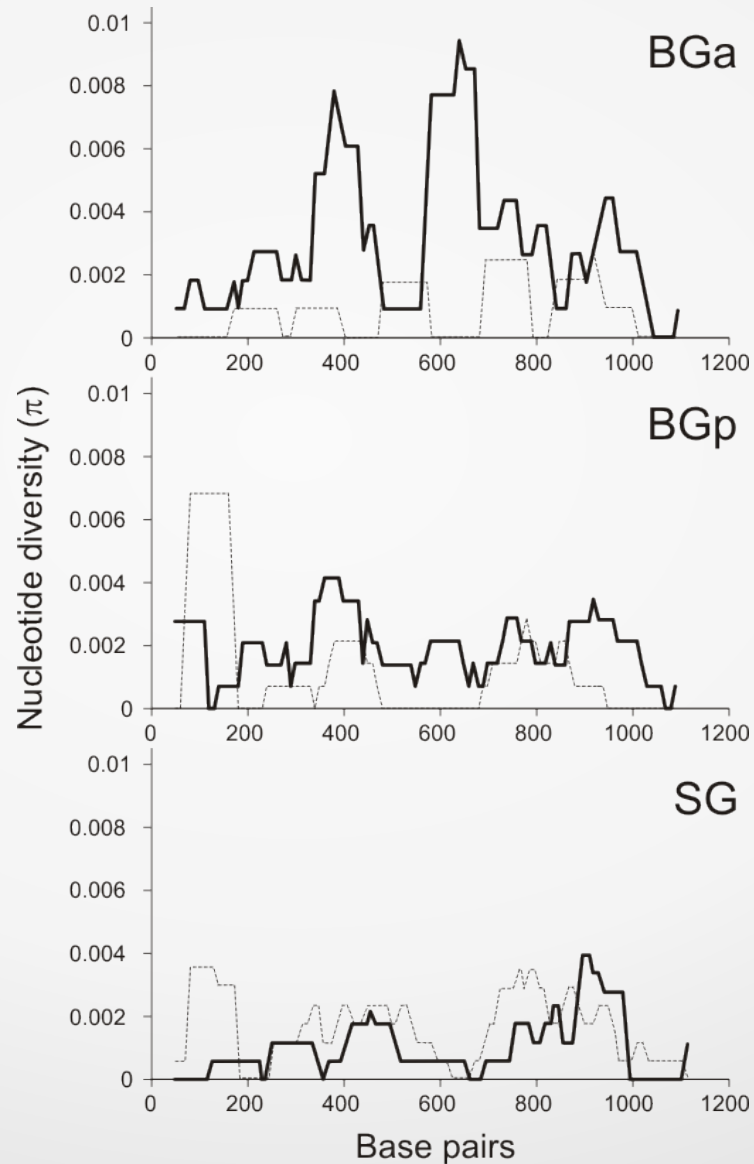
Тест центробежного отклонения замен нуклеотидов

Test of Centrifugal Substitution Bias

Sliding Windows

Nucleotide diversity (π) along the Cytb

Bold solid lines indicate W \rightarrow S mutations, and thin dashed lines indicate S \rightarrow W mutations.



Синонимичные замены влияют на экспрессию
Silent Mutations Influence Protein Production

Выводы Conclusions

We have found some signs of selection, whose action may be related to the regulation of mtDNA gene expression through alterations of mRNA secondary structure. mtDNA gene expression regulation is still poorly understood, and virtually nothing is known about regulation at the mRNA level. If our suppositions are correct, golomyankas can serve as a valuable data source for the study of these processes.