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Molecular Genetics course
Faculty of Sciences-Lebanese University

Molecular Genetics
3rd Year Biology
Course Syllabus

Code	Title	Semester	Credits	C	TS	LS	Total
Biol 321	Molecular Genetics	S5	4	36 h	0	0	36 h

Department of Life and Earth Sciences.

Aim

This course introduces the fundamentals of Molecular Genetics. Mechanisms of gene expression in prokaryotes and eukaryotes will be detailed focusing on the similarities and differences. The structure and organization of genes and genomes as well as the surprising variety of control mechanisms that operate to regulate gene expression will be explained.

Genetics in perspective

There is no biology without genetics! The discipline of genetics provides a set of unifying concepts for teaching all aspects of biology. But more than that, it provides a compelling focus for stimulating interest in learning biology. The study of genetics provides the basis to understand diverse aspects of biology. Genetics has never been a simple task. Genetics has a reputation for being hard to teach and hard to learn. Paradoxally, this is primarily because genetics is fundamentally simple. But "simple" does not necessarily mean "easy." Genetics is "simple" because it can be reduced to an abstract formalism. General principles can explain many specific observations, and predictions can be made with probabilities that can be calculated. But it has been well established that for most students, even for most college undergraduates, learning abstract principles is hard. Understanding genetics is particularly timely and relevant to many major issues of public concern regarding the role of human heredity and individual variation in health-related issues such as cancer, heart disease, alcoholism, and drug addiction. Environmental mutagens and carcinogens, such as ultraviolet radiation, ionizing radiation from radioactive waste and reactor accidents, food additives, agricultural chemicals, and industrial solvents, are common types of risk-versus-benefit controversies. And the most frightening, and threatening health risk of our time, AIDS, can only be understood and controlled through application of techniques and insights from molecular genetics.

Molecular Genetics focuses on the mechanistic details of the different processes pertaining to the flow of information. Replication makes accurate copies of the genetic material; transcription generates messenger RNAs, which are translated into polypeptides by supramolecular complexes, the ribosomes. Proteins fulfill most of the functions a cell can carry out. Regulation of gene expression is crucial to attain harmony and effectiveness. Regulators of all kinds, various regulatory mechanisms and epigenetic modifications form layers of information that tailor gene expression to the needs of the cell. Although accurate, DNA replication is by definition an error-prone process generating mutations at a very low rate. Mutations are the primary source of genetic variation on which natural selection acts through the processes of adaptation and speciation. However, mutations account only for small-scale alterations of the genome; genetic recombination, shuffle the genetic material, create new combinations of alleles, thus accounting for large-scale

changes of the genome. All the mechanisms of genetic recombination are described to further understand their consequences in the light of evolution.

Biotechnology, primarily based on molecular genetics, is offering solutions to many serious problems; solutions which themselves have the potential of becoming new problems. In short, knowledge of genetics is fundamental to understanding biology and essential for understanding many of the most important public issues that we face.

The dramatic progress in molecular genetics, in large part because of technical simplicity, can make teaching more effective: We can use simple microorganisms and uncomplicated methods and techniques. The most recent milestone in biology research is the systemic sequencing of the genomes of a number of model organisms such as the yeasts, *S. cerevisiae* and *S. pombe*, the worm *C. elegans*, the fruit fly *D. melanogaster*, the plant *A. thaliana*, the mouse *M. musculus*, humans, etc. The wealth of genomic data has ushered into the new era of Functional Genomics using large-scale approaches to decipher the function of every single gene; later, models are to be built to explain how the whole system works. This final aim is part of a new discipline baptized "Systems Biology".

Course outline

- ❖ Introduction to Molecular Genetics and Genomics
  - ➢ Discovery of genetic information
  - ➢ DNA and RNA structure
  - ➢ Anatomy of eukaryotic and prokaryotic genomes
- ❖ Genome Replication
- ❖ Gene expression-step 1
  - ➢ RNA synthesis and processing
  - ➢ Regulatory mechanisms
- ❖ Gene expression-step 2
  - ➢ Protein synthesis and processing
  - ➢ Proteome dynamism
- ❖ Genetics of Microorganisms
- ❖ Extra nuclear genomes (organellar genetics)

References

Peter J. Russell. *Igenetics: A Molecular Approach*. **2013**, Pearson Education Limited, ISBN-13:9781292026336.

James D. Watson. *Molecular Biology of the Gene*. **2013**, Benjamin-Cummings Publishing Company, ISBN-13:9780321762436.

Terry Brown. *Introduction to Genetics: A Molecular Approach*. **2011**, Garland Science, ISBN:9780815365099.

Detailed outline of the course

I. Introduction: the nature of the genetic material

I.1. What are the genes at the molecular level?
I.2. Beadle and Tatum experiment in 1942: one gene one enzyme
I.3. Clinical evidence that genes were related to enzymes
  I.3.1. Garrod’s hypothesis of inborn errors of metabolism
  I.3.2. Metabolic Pathways for phenylalanine and tyrosine
I.4. Experiments that prove that DNA is the molecule of heredity
  I.4.1. 1928 Griffith’s transformation experiment
  I.4.2. 1944 Avery, Macleod and McCarty’s experiment
  I.4.3. 1953 Hershey and Chase experiment with bacteriophage T2

- I.5. The discovery of RNA as genetic Material
- I.6. The chemical composition of DNA and RNA
- I.7. The structure of the genetic material
  - I.7.1. A brief history of DNA
  - I.7.2. Chargaff's rules: base composition studies
  - I.7.3. Franklin and Wilkins experiments: X-ray diffraction studies
  - I.7.4. The Double Helix model by Watson and Crick
- I.8. Molecular structure of DNA
  - I.8.1. A, B and Z forms
  - I.8.2. Features of different conformations of the DNA double helix

II. Nucleic acids properties

- II.1. Biological macromolecules are maintained by weak forces
- II.2. DNA stability
- II.3. Structural properties of A-, B- and Z-type of DNA double helix
- II.4. Topology of DNA
  - II.4.1. Relaxed and supercoiled plasmid DNAs
  - II.4.2. Supercoiling and linking number
  - II.4.3. Superhelix winding number and superhelix density
  - II.4.4. DNA Topoisomerases
    - II.4.4.1. Mode of action of a type I topoisomerase
    - II.4.4.2. Mode of action of a DNA gyrase a type II topoisomerase
    - II.4.4.3. Topoisomerases as drug targets
    - II.4.4.4. Types of topological interconversions catalyzed by type II topoisomerases
  - II.4.5. Intercalating agents (IA)
  - II.4.6. IA relieves the stress of (-) supercoils
  - II.4.7. Cruciforms or palindromes
- II.5. Biological significance Differences between DNA and RNA
- II.6. Physical features of DNA
  - II.6.1. Denaturation and renaturation of DNA
  - II.6.2. Dependence of DNA denaturation on GC content and on salt concentration
  - II.6.3. Thermal melting profile (TMP) and hyperchromic shift (HS)
- II.7. Ultracentrifugation techniques
  - II.7.1. Subcellular fractionation of tissue
  - II.7.2. Isopycnic centrifugation and buoyant density of DNA
- II.8. Hydrolysis of nucleic acids
  - II.8.1. Nuclease specificity
  - II.8.2. Restriction enzymes and restriction mapping

III. Anatomy of prokaryotic and eukaryotic genomes

- III.1. Contrast between interphase chromatin and mitotic chromosomes
- III.2. Chromatin structure
  - III.2.1. General properties of histone proteins
  - III.2.2. Stochiometry of core histones in chromatin
  - III.2.3. Chromosome superstructure
- III.3. Eukaryotic genomes
  - III.3.1. C value and C-value paradox
  - III.3.2. Genome sizes and gene numbers for various eukaryotes
  - III.3.3. Genome compactness
  - III.3.4. Sizes of mitochondrial and chloroplast genomes

III.4. Human chromosomes
III.4.1. Condensin and cohesin
III.4.2. Cytogenetics
III.4.2.1. Historical view
III.4.2.2. Chromosomal Mutations
III.4.2.3. Preparation of a karyotype
III.5. Life domaines
III.5.1. There are three distinct domains of life: Archaea, Bacteria and Eucarya
III.5.2. Modern classification
III.5.3. Phylogenetic tree of bacteria
III.5.3.1. Adaptations for growth at extreme temperatures
III.5.3.2. Adaptations for growth at extreme pH
III.5.3.3. Osmotic classes of organisms
III.5.3.4. Oxygen classes of organisms
III.5.4. Anatomy of prokaryotic genomes
III.5.4.1. Examples of genome organization in prokaryotes
III.5.4.2. Features of typical plasmids
III.5.4.2. The *E. coli* genome

IV. DNA replication
IV.1. Introductory remarks: main issues
IV.2. Model for DNA replication
IV.2.1. The plectonemic structure of DNA
IV.2.2. Proposed Models of DNA Replication: semiconservative, conservative and dispersive
IV.2.3. DNA replication is semiconservative
IV.2.3. Meselson and Stahl experiment in 1958
IV.2.3. Harlequin chromosomes
IV.2.3. Taylor-Woods-Hughes experiment in 1957
IV.3. Replication process
IV.3.1. Origin of replication
IV.3.2. Initiation, elongation and termination of DNA synthesis
IV.3.3. Evidence points to bidirectional replication
IV.3.4. Temporal ordering of DNA replication initiation events
IV.3.5. Replication versus transcription
IV.4. Replication of bacterial chromosome
IV.4.1. Motif and consensus sequence
IV.4.2. The *E. coli* origin of replication *oriC*
IV.4.3. Enzymes involved in prokaryotic DNA synthesis
IV.4.4. Properties of DNA polymerases I, II, and III
IV.4.4.1. Subunits of the DNA Polymerase III holoenzyme
IV.4.4.2. Subunit structure of the *E. coli* DNA polymerase III holoenzyme
IV.4.5. Other *E. coli* DNA polymerases
IV.4.6. DNA replication is semi-discontinuous
IV.4.7. Replication of *E. coli* chromosome
IV.4.7.1. DNA synthesis requires an RNA primer
IV.4.7.2. The replication machine or replisome
IV.4.7.3. General features of the replication fork in E. coli
IV.4.7.4. The cycle of lagging strand synthesis: Okazaki fragments
IV.4.7.5. Termination of replication Topoisomerase action

IV.4.8. Regulation of the *E. coli* DNA replication
IV.4.8.1. Helmstetter-Cooper model
IV.4.8.2. Different mechanisms act to prevent rapid replication re-initiation at *oriC*
IV.4.8.3. DNA Methylation and Replication
IV.4.8.4. *E. coli* DNA replication is regulated by DnaA-ATP level
IV.5. Replication of eukaryotic genomes
IV.6. Replication of the yeast *Saccharomyces cerevisiae* genome
IV.6.1. Strategy to identify replication origins in yeast cells: ARS elements
IV.6.2. Initiation of Replication
IV.6.3. DNA polymerases involved in replication: properties
IV.6.4. The notion of processivity
IV.6.5. Enzymology and mechanisms
IV.6.5.1. Similar functions at bacterial and mammalian replication forks
IV.6.5.2. The eukaryotic replication machinery is generally similar to that of *E. coli*
IV.6.6. Chromatin structure and replication
IV.6.6.1. Assembly of new nucleosomes
IV.6.6.2. Structure of SMC proteins
IV.6.6.3. Model for the roles of cohesins and condensins during the eukaryotic cell cycle
IV.6.7. How to maintain the ends of eukaryotic chromosomes
IV.6.7.1. Sequences of telomere repeats and telomerase RNAs in various organisms
IV.6.7.2. Synthesis of telomeric DNA by telomerase
IV.6.7.3. Regulation of the telomerase activity
IV.6.8. Variations on the semi-conservative mode of replication
IV.7. The eukaryotic cell cycle
IV.7.1. The phases of a eukaryotic cell cycle
IV.7.2. Cell cycle control
IV.7.2.1. Characterization of the cell cycle machinery
IV.7.2.2. Regulators of cell cycle: cyclins and cyclin-dependent kinases (CDKs)
IV.7.2.3. Identification and experimental basis of cell cycle regulatory factors
IV.7.2.4. Functions of MPF (cyclin b-cdc2/cdk1)
IV.7.2.5. Polyubiquitination of mitotic cyclins
IV.7.2.6. Mechanism for restriction point regulation
IV.7.2.6.a. Role of E2F and Rb protein in regulation of RP passage
IV.7.2.6.b. E2F transcription factor family
IV.7.2.7. Mechanism for the role of APC in initiating anaphase
IV.7.2.8. Regulation of sister chromatid pairing by the cohesin complex
IV.7.3. Quality of the cell cycle: checkpoints
IV.7.3.1. Oncogenes and tumor suppressor genes (TSP)
IV.7.3.2. Role of p53 in G1 checkpoint arrest
IV.7.3.3. Oncogenes/proto-oncogenes and oncogenic viruses
IV.7.3.4. The hallmarks of cancer/ cancer and growth related factors
IV.7.3.5. Ras proto-oncogenes
IV.7.3.6. TSP functions
IV.7.4. Regulation of the cell cycle
IV.7.4.1. Replication licensing factors
IV.7.4.2. Preventing re-replication/ regulation of pre-RC assembly
IV.7.4.3. Regulation of pre- replication complexes

IV.7.4.4. Just-in-time synthesis vs. just-in-time-assembly
IV.7.4.5. Dynamic modules
IV.7.4.6. Endoreplication
IV.7.4.6.a. Endoreplication without cytokinesis
IV.7.4.6.b. Endoreplication without completion of mitosis and cytokinesis: polyteny and polyploidy

V. Transcription: the process

V.1. Important differences between transcription and DNA replication
V.2. How to access the genome
V.2.1. Functional domain and structural domain
V.2.2. Insulators overcome the positional effect
V.2.3. LCR (Locus Control Regions)
V.2.4. Chromatin modification and genome expression
V.2.5. Histone Modifications determine chromatin structure
V.2.6. Relationship of chromatin organization and gene expression
V.2.7. Nucleosome remodeling
V.2.8. DNA methylation
V.3. Transcription: the process
V.3.1. Synthesis of RNA on a DNA template strand
V.3.2. Promoter, RNA-coding sequence, and terminator regions of a gene
V.3.3. Transcription initiation is a key control in gene expression
V.3.4. RNA Polymerases and the transcription cycle
V.3.5. Enzymology and process
V.4. Transcription in *E. coli*
V.4.1. *E. coli* RNA Pol. Holoenzyme
V.4.2. Transcription in details
V.4.3. Promoter definition
V.4.4. Sequences of *E. coli* promoters
V.4.5. Initiation of polymerization
V.4.6. Chain elongation/two models
V.4.7. A model of the bacterial transcription elongation complex/sliding clamp model
V.4.8. Chain termination/Rho-independent and Rho-dependent termination
V.5. Transcription in Eukaryotes
V.5.1. Functions of the three eukaryotic nuclear RNA polymerases
V.5.2. Yeast RNA polymerase II subunits
V.5.3. Eukaryotic promoters
V.5.4. Transcription mechanism
V.5.4.1. Initiation at different eukaryotic RNA polymerase promoters
V.5.4.2. Promoter clearance
V.5.4.3. Elongation factors for mammalian RNA polymerase II
V.5.4.4. A new set of factors stimulate Pol II elongation and RNA proofreading
V.5.4.5. Functions of the human general transcription factors (GTFs)
V.5.4.6. Mediator consists of many subunits, some conserved from yeast to human
V.5.4.7. Termination in eukaryotes
V.5.5. Stimulation of transcription by activator binding to an enhancer

VI. Transcription: regulation

VI.1. Principles of transcriptional regulation
VI.1.1. Gene expression is controlled by regulatory proteins

VI.1.2. Action at a distance and DNA looping
VI.1.3. DNA-bending protein can facilitate interaction between DNA-bending proteins
VI.2. Transcription regulation in *E. coli*
VI.2.1. Bacteria promoters
VI.2.1.1. The σ factor mediates binding of polymerase to the promoter
VI.2.1.2. Holoenzymes with different promoter-binding specificity
VI.2.1.3. Alternative σ factors control the ordered expression of genes in a bacterial virus
VI.2.1.4. NtrC and MerR: transcriptional activators that work by allostery rather than by recruitment
VI.2.2. Principles of transcriptional regulation: initiation, antitermination and attenuation
VI.2.3. Paradigm of operons
VI.2.3.1. Repressor and operator
VI.2.3.2. Induction vs repression
VI.2.3.3. Metabolic signals and repressor activity
VI.2.3.4. Positive and negative circuits
VI.2.3.5. Lactose operon: inducible (in details)
VI.2.3.6. The *araBAD* operon: inducible (in details)
VI.2.3.7. The *trp* operon: repressible (in details)
VI.2.4. Diversity of mechanisms: DNA:protein interactions, protein:protein interactions, and small molecules
VI.3. Transcription regulation in eukaryotes
VI.3.1. Operons in eukaryotes
VI.3.2. RNA Pol. II promoters/modules/response elements/enhancers/silencers
VI.3.2.1. Insulators block activation by enhancers
VI.3.2.2. Activation of transcription initiation in eukaryotes by recruitment of the transcription machinery
VI.3.2.3. Eukaryotic Regulators
VI.3.2.4. Modular organization of transcriptional activators
VI.3.3. Activation of transcription through direct tethering of mediator to DNA
VI.3.4. Combinatorial gene regulation
VI.3.4.1. The human β-interferon enhanceosome
VI.3.4.2. Mating-type genes
VI.3.4.3. How a TF enhances transcription initiation by RNA Pol. II?
VI.3.4.4. Activators work together synergistically to integrate signals
VI.3.5. Local alterations in chromatin structure directed by activators
VI.3.6. Control of activity of TFs
VI.3.7. Signal-transduction pathways
VI.3.7.1. Two-component signaling system
VI.3.7.2. Mechanism of chemotaxis response
VI.3.7.3. Signal transduction and the control of transcriptional regulators/the MAP kinase pathway

VII. RNA processing
VII.1. Recent view of gene expression
VII.2. Coding and non-coding RNA
VII.2.1. Transcriptome
VII.2.2. Non-coding RNA in bacteria

VII.2.3. Dealing with aberrant termination
VII.3. RNA processing events
VII.3.1. Bacterial mRNA
VII.3.2. mRNA end modification in eukaryotes/capping and polyadenylation
VII.3.3. Exons and introns in eukaryotes
VII.3.3.1. Split genes and intron splicing/features of split genes
VII.3.3.2. Types of introns/consensus sequences of introns
VII.3.3.3. Splicing mechanism/splicing machinery
VII.3.3.4. Dynamic changes in spliceosome composition direct pre-mRNA splicing
VII.3.3.5. The exon definition hypothesis: role of SR proteins
VII.3.3.6. Group I and group II introns/splicing mechanism
VII.3.3.7. Other types of introns
VII.3.4. Chemical modification of RNAs
VII.3.5. RNA editing/examples and mechanisms
VII.3.6. Cutting events in eukaryotes and prokaryotes
VII.3.7. Alternative splicing
VII.3.7.1. Different modes of alternative splicing
VII.3.7.2. Generating protein diversity from the 'small' genome/examples
VII.3.7.3. Diversity by alternative promoters/polyadenylation
VII.3.7.4. Causes and consequences of splicing pattern alterations
VII.3.7.5. Regulatory cascade for sex determination in Drosophila and other examples/
VII.3.8. Turnover of RNA
VII.3.8.1. Degradosome in bacteria
VII.3.8.2. Three major pathways for mRNA degradation in eukaryotes
VII.3.8.3. Nonsense-mediated mRNA decay (NMD) an mRNA surveillance system
VII.4. Transport through the nuclear pore

VIII. Protein synthesis
VIII.1. Informational gap
VIII.2. Elucidation of the genetic code
VIII.2.1. Cell-free protein synthesis
VIII.2.2. Triplet binding assay
VIII.3. General features of the genetic code
VIII.4. Variations to the universal code
VIII.5. Context-dependent codon reassignment
VIII.6. Key components in protein synthesis
VIII.7. Aminoacylation of tRNAs
VIII.8. Wobble hypothesis
VIII.9. Codon usage
VIII.10. Ribosome structure in prokaryotes and eukaryotes
VIII.11. Protein synthesis in details
VIII.12. Protein synthesis in *E. coli*
VIII.12.1. Initiation phase/initiation factors
VIII.12.2. Ribosome-dependent GTPase activity of IF2
VIII.12.3. Roles of IF1 and IF3 in ribosome dissociation
VIII.12.4. Elongation phase/3-step cycle/elongation factors
VIII.12.5. Termination phase/release and ribosome recycling factors in bacteria

VIII.12.6. Polysome structure
VIII.13. Protein synthesis in eukaryotes
VIII.13.1. Initiation phase/properties of the eIFs
VIII.13.2. Regulation of eukaryotic translation via phosphorylation of eIF2
VIII.13.3. Regulation of translation during viral infection
VIII.13.4. Regulation of poly A binding protein activity
VIII.13.5. Elongation phase/termination phase
VIII.14. Unusual events during elongation/programmed frameshifting/translational slippage/translational bypassing
VIII.15. Dealing with aberrant termination
VIII.16. Premature termination (NAS and NMD models in eukaryotes)

IX. Processing of the proteome

IX.1. Protein folding
IX.1.1. Protein Denaturation
IX.1.2. Spontaneous folding
IX.1.3. Protein unfolding/refolding
IX.1.4. Folding pathways
IX.1.5. Folding of large proteins is assisted by chaperones
IX.2. Protein splicing
IX.2.1. Why inteins have not they become extinct?
IX.2.2. Similarities between group I, group II and intein homing
IX.3. Posttranslational chemical modifications
IX.4. Proteolytic cleavage or cutting
IX.5. Protein turnover/ubiquitin pathway
IX.6. Protein kinesis
IX.6.1. Destinations for newly translated polypeptides in a eukaryotic cell
IX.6.1. Secretory pathway
IX.7. Protein synthesis inhibitors

X. Genetics of micro-organisms

X.1. Model Organisms/*E. coli* and *S. cerevisiae*
X.2. Features of microbial genetics
X.2.1. Identifying bacterial mutants
X.2.2. Beadle and Tatum experiment revisited
X.3. Transfer of genetic material
X.3.1. Lederberg and Tatum experiment
X.3.2. Sexual conjugation in bacteria
X.3.2.1. Chromosome transfer: formation of Hfr strains
X.3.2.2. Genetic map of the F (fertility) plasmid of *E. coli*
X.3.2.3. Mapping with interrupted mating technique
X.3.3. Other bacterial sexual processes/transduction and transformation
X.3.3.1. What is a merozygote?
X.3.3.2. Phages-generalized transduction/phages-specialized transduction
X.3.3.3. Transformation under natural conditions
X.3.3.4. Transformation and competence
X.4. Genetic recombination
X.4.1. Different categories: homologous or general recombination/site-specific recombination/transposition/illegitimate recombination
X.4.2. General recombination

X.4.2.1. Recombination and evolution
X.4.2.2. Weigle and Meselson experiment in 1961
X.4.2.3. Recombination and crossing-over
X.4.3. Models of recombination
X.4.3.1. Holliday model
X.4.3.2. Meselson and Radding model
X.4.3.3. Biochemistry of recombination
X.4.3.4. RuvA, B and C can catalyze branch migration, mobilize holiday junctions
X.4.3.5. Structure and Mechanism of the RecA protein from *E. coli*
X.4.4. Double-strand break model and gene conversion
X.4.5. A modified version of Meselson-Radding model accounts for gene conversion
X.4.6. Site-specific recombination/integration
X.4.6.1. Repeat orientation determines recombination outcome
X.4.6.2. Conservative site-specific recombination (CSSR) can generate three different types of DNA rearrangements
X.4.7. Transposition: replicative vs conservative
X.5. Lytic and lysogenic pathways of bacteriophages
X.5.1. Alternative patterns of gene expression control lytic and lysogenic growth
X.5.2. Phage genomes/cascade of regulatory controls
X.5.3. Life cycle of phage Lambda (λ)
X.5.3.1. Bacteriophage lambda genome/genetic switch
X.5.3.2. Lytic pathway in details
X.5.3.3. Lyzogeny in details
X.5.3.4. Prophage induction
X.5.3.5. Expression of *int* and *xis* genes
X.5.3.6. How to make the right decision?
X.5.4. SOS response/induced and uninduced states/functions of SOS genes/prophage induction
X.5.5. Role of genetic switches
X.6. DNA repair systems

XI. Genetics of organelles
XI.1. Model of cellular invasion
XI.2. How many origins for life?
XI.3. Emergence of eukaryotes
XI.4. Endosymbiotic theory
XI.4.1. Background to the endosymbiont hypothesis
XI.4.2. Eukariotic cells evolved from prokaryotes in several stages
XI.4.3. Fates of genes in endosymbiosis
XI.5. Mitochondria and Chloroplasts
XI.5.1. Organelle genomes
XI.5.2. Map of human mtDNA showing the pattern of transcription
XI.5.3. The limited autonomy of the mitochondrial genome