The Egyptian Journal of Medical Human Genetics (2012) **13**, 119–125

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com

EDUCATIONAL CORNER OF THE ISSUE

Educational Corner

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Received 12 June 2010; accepted 13 July 2010
Available online 4 February 2012

1. Part I: Basic concepts of medical genetics

1.1. Genetics and life

All life activities in living cells, whether on a molecular level like ATP production, a cellular level like cell division, a tissue level like muscle contraction or on a whole organ level like hearing for instance, are mediated via a very large number of inter-related metabolic networks. A metabolic network is defined as a cascade of controlled biochemical reactions and biophysical alterations that transform one, or more, substrate to one, or more, products. In human cells, nearly 4100 (four thousand and one hundred) of these networks have been delineated (Fig. 2) [1].

Each network consists of a very large number, sometimes thousands, of proteins, mostly enzymes, and other non-protein factors, all acting cooperatively in a sequence to perform specific biochemical and physiological functions. Proteins and enzymes which are the major mediators and determinants of all metabolic networks in living cells are synthesized under direct and strict regulation of the genetic material. The structural genes, which are the major component of the genetic material, are primarily concerned with controlling and regulating the synthesis of proteins, which in turn control and regulate all life activities in cells. Hence, though the genetic material controls and encompasses the whole spectrum of life processes in living cells, the proteins are the actual and direct mediators of these life processes. This inter-relation between the genetic material, proteins and life activities can be represented in (Fig. 1) that summarizes the central dogma of molecular biology [1].

Fig. 2 illustrates the concept of metabolic networks in life activities.

2. Structure of the genetic material

The building components of the genetic material in all living creatures are the nucleic acids. There are two main categories of nucleic acids: DNA or deoxyribonucleic acid and RNA or ribonucleic acid. With the exception of RNA-viruses which have their genome composed solely of RNA, all living creatures have DNA as their sole genetic material in addition to RNA as well.

Nucleic acids are very long unbranched hetero-polymers composed of large number of similar monomers: the nucleotides, which are the building blocks of the nucleic acids. Each nucleotide is composed of a phosphate group attached to a 5-carbon atom ribose sugar to which is attached a nitrogenous base. Five different bases participate in the formation of five different nucleotides that constitute the building blocks of nucleic acids. The bases are either purine bases: adenine (A) and guanine (G), or pyrimidine bases: cytosine (C), thymine (T), and uracil (U). The nucleotides are usually referred to by the type of base they contain, hence we have (T), (C), (G), (A) and (U) nucleotides. The first four nucleotides are found exclusively in DNA whereas the last four nucleotides exist in RNA (Fig. 3) [2].

Nuclear DNA normally exists as a linear unbranched double stranded helix composed of two strands, each strand is a linear hetero-polymer of the four types of nucleotides referred

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Peer review under responsibility of Ain Shams University.
doi:10.1016/j.ejmhg.2011.11.002

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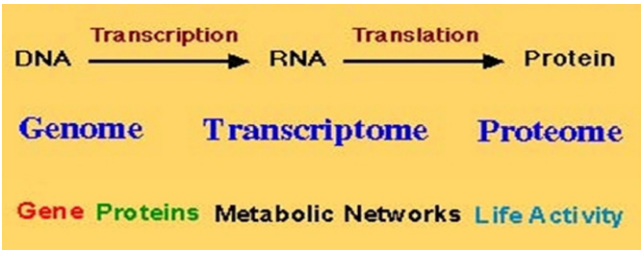

Figure 1 The central dogma of molecular biology.

to. Each nucleotide is attached to the two adjacent nucleotides via phospho-di-ester bonds between its phosphate group and the sugar of the adjacent nucleotide, i.e. the phosphate of one nucleotide is attached to the carbon no. 5 of the sugar of its adjacent nucleotide, whose phosphate in turn is linked to the carbon no. 3 of the sugar of the next nucleotide, and so on, so that a phosphate–sugar–phosphate–sugar, etc. linear strand, forms the backbone of the DNA, with the nitrogenous bases attached to the sugar through a glycosidic linkage, projecting at nearly right angles to the level of this backbone. Accordingly, the direction of phosphate–sugar bonding on one strand goes in a 5′ to 3′ direction, whereas the direction of phosphate–sugar bonding on the other complementary strand goes in the opposite 3′ to 5′ direction. This particular arrangement, referred to as DNA strand polarity, is important because gene transcription always proceeds in a 5′ to 3′ direction. The two strands of DNA are tightly attached to each other by hydrogen bonds between the nitrogenous bases of each opposing nucleotide pair at the same position of the DNA strands. This base bonding normally happens between A of one base and T of the opposing base or between C of one base and G of the opposing base. This specific bonding between particular bases is known as base complementarity and is very important for integrity of DNA structure, stability, and function [3].

Normally, DNA does not exist *per se*. It is wrapped by, and associated with, DNA-binding proteins of two classes: the histones and the non-histone proteins. Histones are small proteins with a very high proportion of positively charged amino acids (lysine and arginine), this characteristic helps tight binding to the highly negatively charged phosphate of the DNA. This tight bonding plays a crucial role in maintaining DNA–Histone association necessary for support, protection, and regulation of DNA structural and functional integrity. There are five types of histones: small, highly conserved nucleosomal histones (H2A, H2B, H3, and H4) and the H1 histones. The nucleosomal histones form a specific disk-shaped complex of eight proteins containing two copies of each of the four nucleosomal histones known as the histone octamer. This histone octamer forms a protein core around which the double-stranded DNA helix is wound twice. This characteristic DNA–Histone complex is known as the nucleosome. The histone H1 molecules, of which there are about six closely related subtypes in eukaryotic cells, are thought to be responsible for associating or binding nucleosomes together thus imparting to the DNA–Histone complex its fibrillar or linear strand conformation [4].

RNA, or ribonucleic acid, has the same basic design of a sugar–phosphate backbone with a nitrogenous base linked to the sugar. However, it differs from DNA in many aspects:

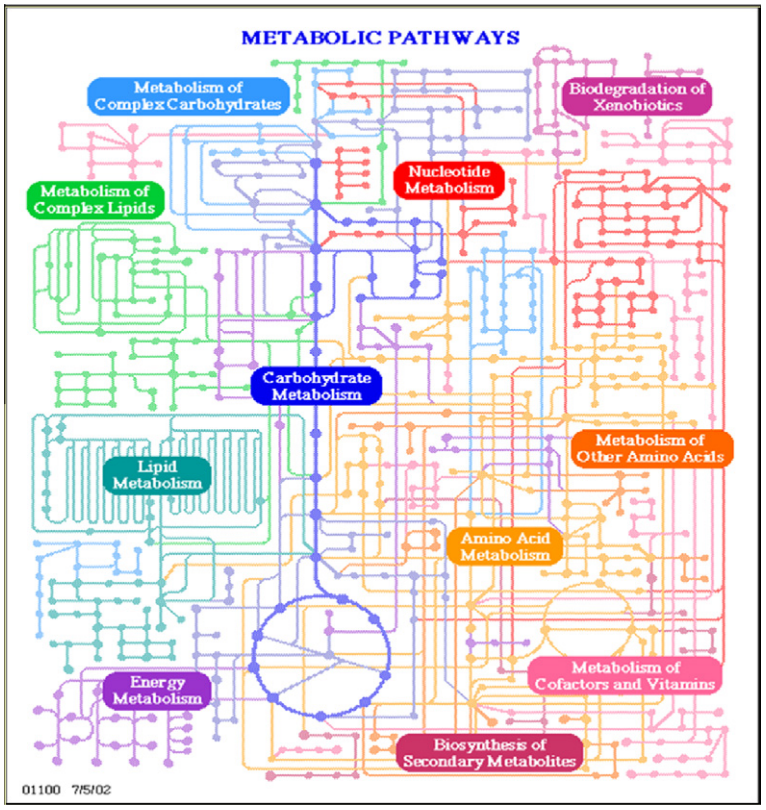

Figure 2 The concept of metabolic networks (http://manet.illinois.edu/pathways.php – image source from KEGG).

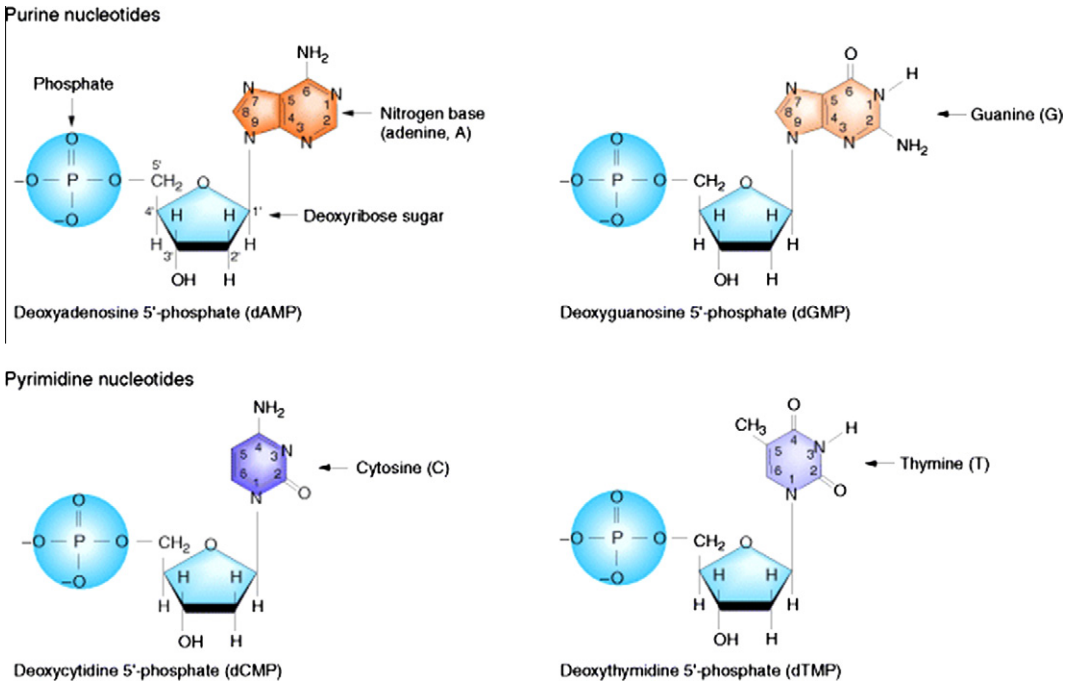

Figure 3 The building nucleotides of DNA (http://www.ncbi.nlm.nih.gov/books/NBK21261/).

1. DNA normally exists in the nucleus as linear double stranded helix and in the mitochondria as circular double stranded molecule, whereas RNA normally exists in the nucleus, mitochondria and cytoplasm as linear single strand.
2. The sugar in DNA is 2-deoxy-ribose, whereas it is ribose in RNA.
3. DNA is composed of A, G, C and T, whereas RNA is composed of A, G, C and U.
4. RNA is usually single stranded, not a double helix. One consequence of this is its ability to form complex three-dimensional molecular shapes than can be a double-stranded DNA. It can fold into characteristic secondary and tertiary structures that account for its diverse functional activities.
5. Whereas DNA normally exists as single functional type that performs both replication and transcription, there are at least four different functional subtypes of RNA: primary or heterogeneous nuclear (hnRNA) which is the primary transcript of the gene with information coded by both exons and introns, small nuclear RNA (snRNA) involved in the process of splicing of primary or heterogeneous nuclear RNA thus producing the semifinal carrier of genetic information or messenger RNA (mRNA) which is responsible for carrying these information for protein synthesis to the site of synthesis in the cytoplasm, ribosomal RNA (rRNA) responsible for decoding or translation of the genetic information in mRNA to specific amino acid sequence in the synthesized protein, transfer RNA (tRNA) responsible for getting the required amino acids for protein synthesis from the metabolic pool of the cell and transporting them to the site of translation and synthesis in the ribosomes, guide RNA (gRNA) involved in RNA editing, small cytoplasmic RNA (scRNA) that participates in protein trafficking and targeting in the cell, and ribozymes or catalytic RNA molecules with specific enzymatic activities (Fig. 4) [2].

3. Mitochondrial DNA (mtDNA)

Mitochondrial DNA normally exists as closed circular double stranded molecules, each consisting of about 16,000 base pairs, with associated proteins similar in composition to those associated with nuclear DNA (nDNA). Contrary to nDNA, mtDNA exists as separate discrete structures, or molecules, within the mitochondrial matrix with each mitochondrion containing multiple copies, sometimes tens or hundreds, of these molecules. Accordingly, each human cell contains hundreds of mitochondria and thousands of mtDNA molecules sharing the same complement of genes in all cells (Fig. 5) [4].

4. Structural organization of the human genome

The human genome, defined as the total sum of the genes or the genetic material in the cell, consists of genes in addition to other non-genic or gene-related components. Each species has its own specific genome that differs from the genome of any other species as regards the number of genes, their cellular distribution and the size of the genome itself, among many other inter-species differences. In human cells, the human genome is unequally distributed in the cell between a major part (99.9999%) that comprises the nuclear genes, i.e. genes organized as chromosomes in the cell nucleus, and a minor, albeit vital and indispensable, part (0.0001%) that comprises the mitochondrial genes located inside the mitochondria in the cytoplasm.

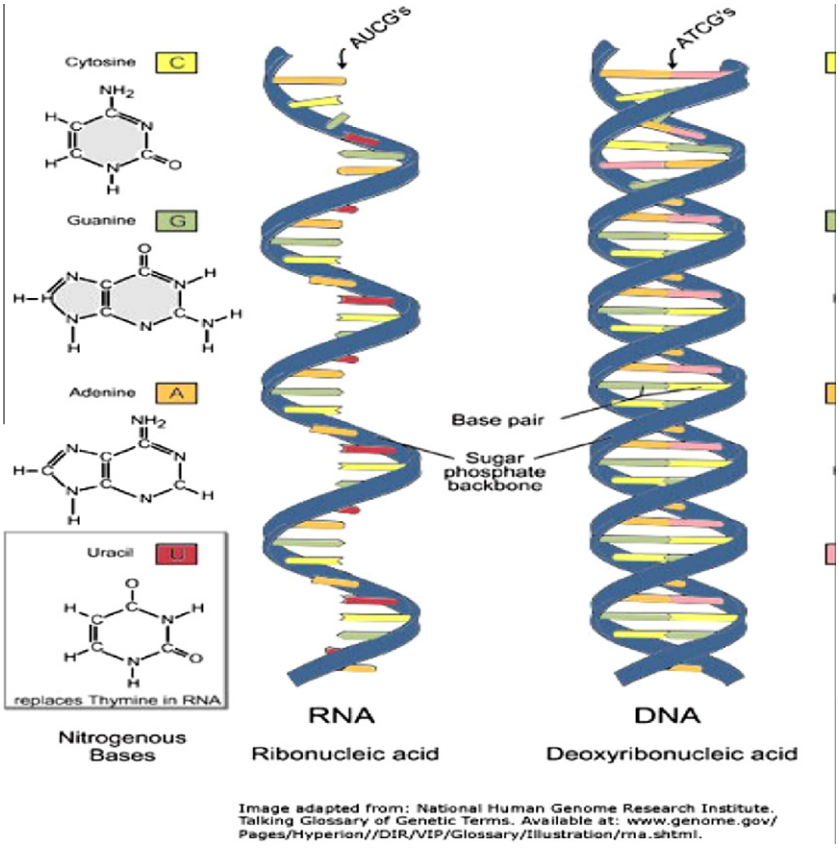

Figure 4 Comparative structural differences between DNA and RNA – images adapted from National Human Genome Research Institute.

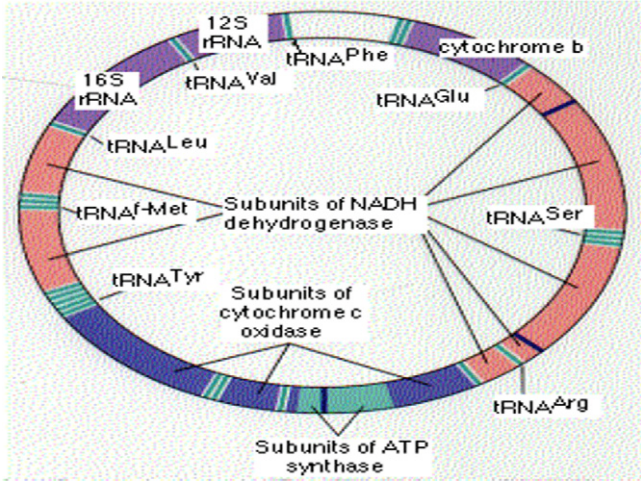

Figure 5 Mitochondrial DNA (http://proyectosadnhisp-anos.bravehost.com/mitoDNA.html).

The nuclear genes in each human germ cell, ovum and sperm, are organized into a set of 23 separate chromosomes known as the haploid set of chromosomes. Upon fertilization, both haploid sets of the sperm and the ovum constitute a diploid set consisting of their 46 chromosomes that characterizes the nuclear genes' component of the zygote as well as of all somatic cells descendant from it. The mitochondrial genes' component in the zygote derives mainly from the mitochondria present in the ovum (about 100,000 mitochondria), with a minor fraction (about 100 mitochondria) being derived from the sperm. In somatic cells, the mitochondrial genes' component or mitochondrial DNA (mtDNA) is distributed unevenly between the mitochondria of the cell and consists of varying numbers, tens to thousands, of small circular DNA molecules within each mitochondrion [5].

Whereas the number of mitochondrial genes in each circular DNA molecule within the mitochondrion figures around 37 genes with an estimated 16,569 nucleotides, the number of nuclear genes organized as chromosomes is estimated to lie between 25,000 and 40,000 genes. Only a small fraction, 3–5%, of this DNA is thought to code for proteins.

Each DNA structure is a linear double-stranded polymer; however, it is usually referred to as a single molecule, so there are 46 molecules of DNA comprising the 46 chromosomes in somatic cells and half this number in germ cells. The human haploid genome contains around 3,000,000,000 nucleotide pairs and the diploid genome of somatic cells contains double this amount of nucleotides (Fig. 6) [2].

5. Structure of human genes

The gene is defined as the functional unit of the genome. It consists of a specific linear segment of the active, functional or sense strand of the double stranded DNA, with a conserved characteristic unique number sequence of bases (or

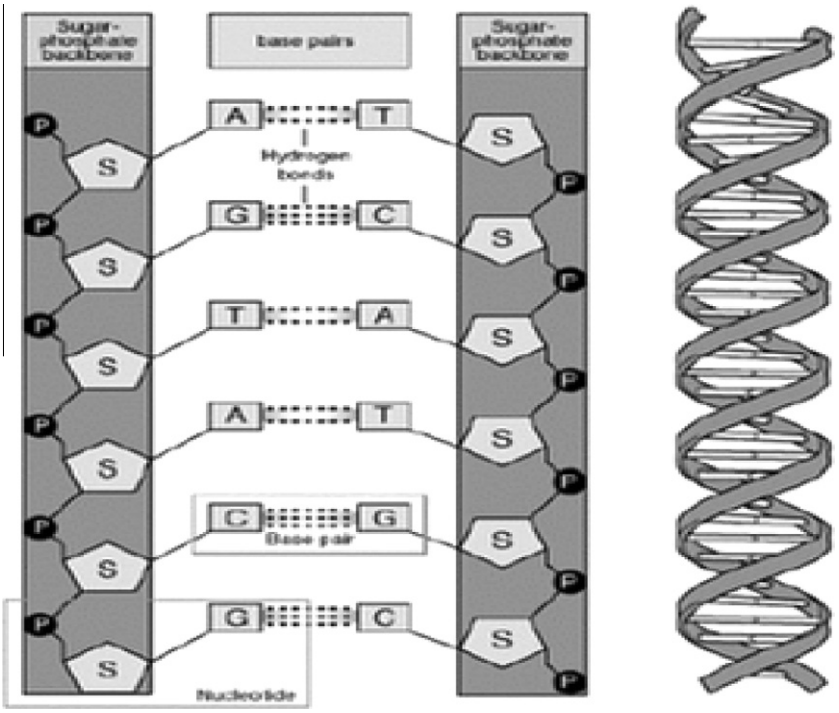

Figure 6 Helical structure (right) and base complementarity (left) of DNA (image credit: cnx.org/content/m12382/latest/).

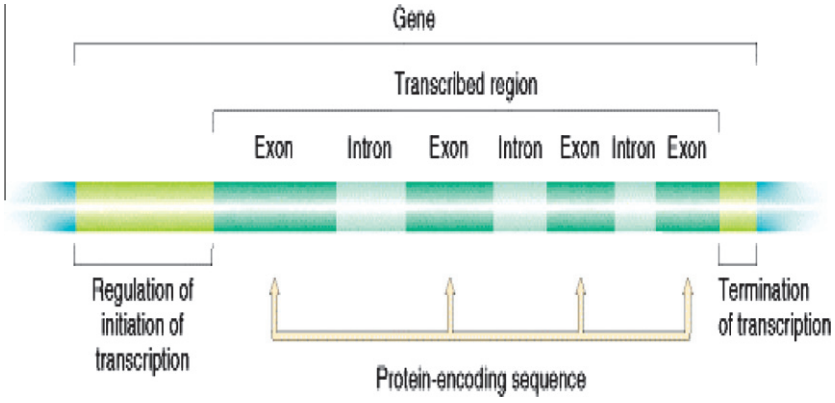

Figure 7 General scheme of gene structure.

nucleotides). Genes are arranged in a linear sequence along the DNA. Genes differ from each other according to the number and unique arrangement of their bases. This specific sequential order of bases along the gene imparts to each gene its functional and structural identity. Whereas the nucleotide is the structural unit of the gene, the codon is the functional unit of the gene, and is defined as a sequence of three successive bases along the gene that codes for a specific amino acid in the final gene product, i.e. a polypeptide chain. Some codons do not code for any amino acids and are termed stop or termination codons. Also, some amino acids are coded or defined by more than one codon, a phenomenon known as degeneracy of the genetic code, but no single codon can code for more than one specific amino acid. The general design of most eukaryotic genes consists of an operator segment, a specific sequence of bases at the start end of the gene, responsible for regulating gene function by beginning or suppressing gene expression, and a variable number of exons, expressing segments or specific sequences of the gene that are actively transcribed and always code for specific amino acids in the final gene product or the polypeptide chain, and a variable number of introns, intervening segments or specific sequences of the gene that are actively transcribed but in most cases do not code for specific amino acids in the final gene product, due to their excision from the primary or hnRNA. Exons and introns alternate in sequence along the length of the gene, and their number and arrangement is characteristic of each gene. All these segments are composed of nucleotides, it is the specific sequence and arrangement of bases, as well as the site along the gene, which imparts to each of these components its functional role as an operator, an exon, or an intron (Fig. 7) [1].

Genes are classified to three major groups, structural genes, regulatory genes and master genes. Whereas the great majority of human structural genes are directly involved in coding for,

and synthesis of proteins, a significant minority, about 5% of the genes or perhaps 3000–4000 genes in all, encode mature RNA molecules, other than mRNA, of diverse function, e.g. tRNA, rRNA and snRNA involved in translation, polypeptide chain synthesis, and post-translation trafficking of proteins, respectively. The mitochondrial genome is exceptional in that 65% of its genes encode RNA necessary for mediating many mitochondrial functions [4].

Proteins produced by structural genes also, can be divided into structural proteins that participate in building different cellular components, e.g. cell membrane and cytoskeleton proteins, and catalytic proteins or enzymes concerned with mediating metabolic activities of the cell. Regulatory genes, on the other hand, are responsible for controlling and regulating the functions of structural genes. Their products can initiate, maintain, and terminate the activity of structural genes according to the needs of the cell. They, also, organize the functions of structural genes through modifying, enhancing or silencing their rate and timing of transcription. Regulatory genes control diverse cellular functions necessary for normal life, e.g. control of cell cycle and cell division, control of normal embryonic development, and repair of DNA mutations.

Mitochondrial genes have certain characteristics that differentiate their structural and functional specificities from those of nuclear genes:

1. Whereas most nuclear genes responsible for coding a particular product exist as pairs equally derived from both parents, mitochondrial genes exist in multiple similar copies, sometimes hundreds or thousands, mediating one and the same function within the cell, and derived, mostly, from the mother.
2. Though there are discrete intervening DNA sequences lying between some of the mitochondrial genes, they do not have recognizable introns within their structure.
3. Each mitochondrial genome consists of 37 genes that code for 37 recognized products. These products comprise 22 tRNA molecules, two rRNA molecules, and 13 proteins which are assembled with other nuclear gene-encoded proteins to constitute the structural proteins and catalytic enzymes that mediate mitochondrial metabolic activities [6].

Appendix A. Part II: MCQ

A.1. MCQs – Medical genetics

Select only the best one answer for each question:

1. New treatments of phenylketonuria include the following EXCEPT:
   A. Neutral amino acids supplementation
   B. Omega 3 and Omega 6 supplementation
   C. Aspartam consumption instead of sugar
   D. Biopterin cofactor
   E. High-dose tyrosine supplementation

2. Peutz-Jeghers syndrome (PJS) is characterized by all of the following EXCEPT:
   A. Gastrointestinal polyposis and mucocutaneous pigmentation
   B. Innate cellular immunodeficiency
   C. Affected individuals are at increased risk for malignancies
   D. Can be diagnosed both prenatally and postnatally by molecular testing
   E. It is inherited in an autosomal dominant manner

3. The term imprinting indicates:
   A. Loss of heterozygosity
   B. Suppression of one parental allele by the other allele
   C. Downregulation of heterochromatin
   D. Differential suppression of genes based on parental origin
   E. Variable timely expression of clinical features

4. Treatment of familial hypercholesterolemia includes all of the following EXCEPT:
   A. LDL apheresis
   B. Portacaval anastomosis
   C. Bile acid sequestrants
   D. Nicotinic acid (niacin)
   E. Zinc supplementation

5. Fibroblast growth factor receptor mutations cause all of the following disorders EXCEPT:
   A. Achondroplasia
   B. Hypochondroplasia
   C. Pseudoachondroplasia
   D. Thanatophoric dysplasia
   E. Crouzon syndrome

6. Reliable diagnosis of hepato-renal tyrosinemia can be attained by:
   A. Measurement of plasma tyrosine level
   B. Measurement of urinary tyrosine level
   C. Measurement of serum NTBC level
   D. Measurement of urinary succinylacetone level
   E. Liver biopsy

7. A true statement about pseudogenes is:
   A. They represent evolutionary remnants of junk DNA
   B. They are found exclusively in heterochromatin regions of chromosomes
   C. They can take over the functions of imprinted genes
   D. Some pseudogenes play a role in gene regulation and expression
   E. They can be identified due to their rich content of A & T nucleotides

8. Peroxisomal disorders include all of the following conditions EXCEPT:
   A. Adrenoleukodystrophy
   B. Acute intermittent porphyria
   C. Adrenomyeloneuropathy
   D. Zellweger syndrome
   E. Hyperoxaluria type I

9. Imprinting underlies the pathogenesis of the following disorders EXCEPT:
   A. Leber optic atrophy

B. Huntington disease
C. Beckwith-Wiedemann syndrome
D. Prader-Willi syndrome
E. Myotonic dystrophy

10. Which of the following functions explains the role of cystic fibrosis protein?
A. ABC transporter protein
B. Signal transduction protein
C. Potassium channel regulator protein
D. Cell cycle regulator protein
E. None of the above

11. New trends in genetic therapies include all of the following EXCEPT:
A. Stem cell therapy
B. DNA demethylating agents
C. Molecular chaperone therapy
D. RNA editing
E. Regulation and control of apoptosis

12. In which of the following phenotypic females does a testis develop?
A. 46, XY with an interstitial deletion of Yp involving the SRY gene
B. 45, X
C. 46, XY with X-linked androgen receptor deficiency
D. 46, XX
E. 46, XY with a point mutation in the HMG domain of the SRY gene

13. Chaperones are responsible for:
A. Participation in RNA splicing
B. Control of tRNA-amino acid binding
C. Regulation of protein trafficking inside the endoplasmic reticulum
D. Regulation of protein assembly and correction of protein misfolding
E. Apoptosis pathways

14. Which of the following genetic therapies would worsen a patient with β-thalassemia major?
A. Increasing fetal Hb gene production
B. Increasing β-globin gene production
C. Increasing α-globin gene production
D. Decreasing α-globin gene production
E. Increasing Δ (delta) Hb gene production

15. Which of the following statements about DiGeorge syndrome is false:
A. It is caused by large deletion on the long arm of chromosome 22
B. Patients suffer recurrent infections secondary to immune deficiency
C. Occurrence is sporadic in about 85% of cases
D. An affected person has a 50% chance of transmitting the condition to his or her child
E. Patients have hypocalcemia secondary to hypercalciuria

Model answers:

1	C	6	A	11	D
2	B	7	E	12	B
3	D	8	B	13	C
4	D	9	C	14	C
5	A	10	D	15	E

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