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Basic concepts of medical genetics

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1. Gene function

The genome of each organism, composed of all genes specific to the organism, is responsible for determining, configuring, and regulating all structural and functional aspects of that organism. These activities are actually mediated by the unique proteome of each organism, i.e. the sum of proteins produced in that particular organism by its own genome. The genomes of different organisms are composed of variable numbers of genes, up to tens of thousands as is the case in human, and can produce variable numbers, up to tens of thousands or even millions, of different proteins required for development and maintenance of all life aspects of the organism. So, the proteome of each organism is determined by its genome. Each of the genes of the genome is responsible for controlling a particular biological function through its product, may be a particular protein or a non-mRNA molecule responsible for mediating that particular biological function. Accordingly, the main function of the gene is the production of a unique product responsible for a specific biological function. Each gene carries in its unique base sequence the genetic information necessary for production of its gene product or its unique protein synthesized in the cell cytoplasm or cytosol [1].

The central dogma of molecular biology, or the frame of mediation of life processes at the gene–protein level, as illustrated in (Fig. 1), entails that genes regulate synthesis of proteins which mediate all life activities of living organisms. Actually, this is the major function of most genes. Genes which directly regulate protein synthesis are called structural genes. The functions of these structural genes are conducted under strict supervision of regulatory genes which regulate switching on, or activation, and switching off, or suppression, of structural genes so that the proper amount of proteins necessary for mediating physiological processes is synthesized at proper times. Proper control of these temporal aspects of gene function is of utmost importance for fine control, regulation and cooperation of the very large number of metabolic networks of the cell. Still, a third group of genes, master genes or housekeeping genes, function in a continuous manner to ensure maintenance and persistence of life-dependant processes. Examples of these processes include cell growth, cell division, ATP production and apoptosis. Continuous monitoring of these life-dependant activities is mandatory to keep life activities in living organisms [1].

Structural genes regulate protein synthesis via the genetic information, or the genetic code, which is the information contained within the specific arrangement of the nucleotides, or bases, of the gene that determine the gene function(s). It is designed to function in a specific way so that each three nucleotides in sequence along the gene, known as the codon, which is the functional unit of the gene, define a single specific amino acid in the protein synthesized under regulation of the gene. There are 64 known codons: 61 functional codons which define specific amino acids in the proteins, and three termination or stop codons that do not define any amino acids in the protein (Fig. 2). Rather, they determine the end point of the synthesized protein.

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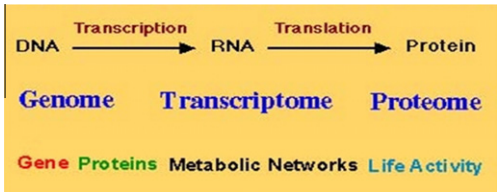


Figure 1 Central dogma of molecular biology.

The genetic code is universal, it is used by all known forms of life, albeit, minor variations do exist for codes of mitochondria, candida, bacteria, mycoplasma and archaea [2].

Though all genes are composed of the same four nucleotides, A–T–C– and G, each gene has its own functional specificity which is determined by the physiological function(s) mediated by its product; insulin gene regulates the synthesis of insulin, hemophilia gene regulates the synthesis of anti-hemophilic globulin, and collagen gene regulates the synthesis of collagen, and so on. Accordingly, the functional specificity of the gene depends on its specific and peculiar codon sequence of its exons. The codon sequence of the gene, which reflects the specific base sequence or arrangement of nucleotides along the gene, dictates the specific amino acid sequence of the synthesized protein leading to production of a unique protein, thus imparting to each gene its functional specificity [3].

Gene function is conducted via a sequence of stages. At least five of these stages have been defined. They begin with switching on, or activating, the gene and end with production of the required gene product or protein. The well defined stages of function of structural genes include the following stages (Fig. 3):

1. Gene activation.
2. Transcription.
3. Post-transcription modifications.
4. Translation.
5. Post-translation modifications.

2. Gene activation

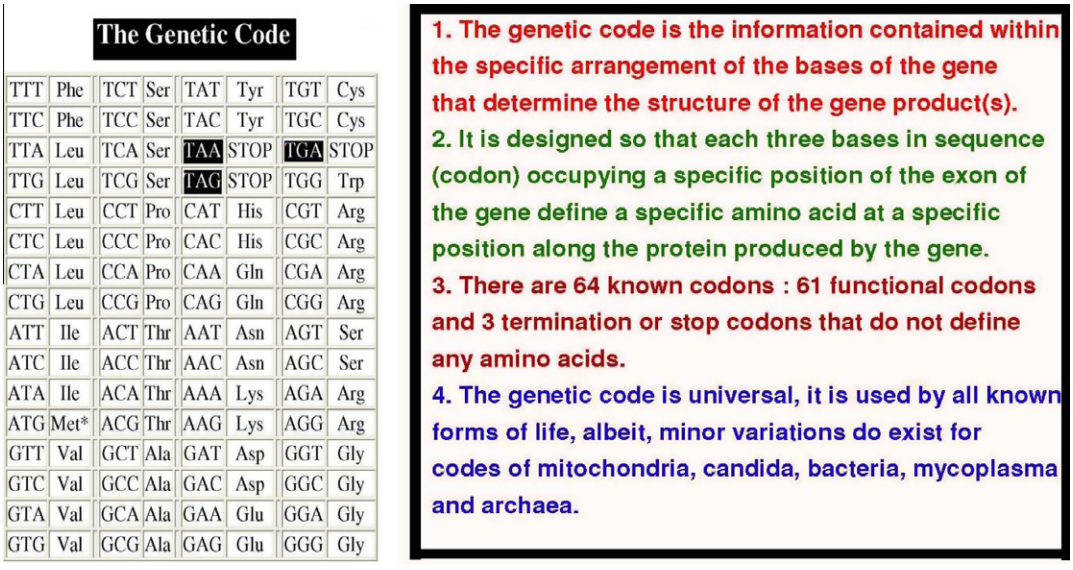
Activation of the gene is the first stage of gene function. It happens via a complex series of modifications involving the DNA and the DNA-associated proteins, followed by a sequence of interactions between specific activating components, microRNA and nucleoproteins, and the promoter of the gene. These processes are triggered and regulated by, still largely unknown, temporal mechanisms and specific factors synthesized by, or under control of, regulatory genes.

3. Transcription

Since nuclear genes do not leave the nucleus to the cytosol because the DNA-associated proteins can be digested by cytosolic enzymes leading to its damage, the second stage of gene function, or transcription, comprises transferring the information contained within the gene, and necessary for protein synthesis in the cytoplasm, to a messenger molecule that can be synthesized whenever needed to, leave the nucleus to the site of protein synthesis in the cytoplasm, offer its information to the protein synthesis machinery and degraded after finishing its mission. This stage is termed transcription since a transcript of the gene carrying its information is synthesized in the nucleus. Transcription entails synthesis of a single stranded mRNA molecule with a base sequence complementary to that of the gene. In the cytoplasm, decoding, reading and interpretation of this sequence to determine the proper amino acids composing the protein product of the gene is accomplished by the protein synthesis system in the cytoplasm which comprises too many interacting factors including the ribosomes, ribosomal RNA, transfer RNA and many others (Fig. 4).

4. Post-transcription modifications

Post-transcription modifications refer to the modifications that alter the structural configuration of the freshly transcribed mRNA molecule. These changes are mandatory in order to



The Genetic Code

TTT	Phe	TCT	Ser	TAT	Tyr	TGT	Cys
TTC	Phe	TCC	Ser	TAC	Tyr	TGC	Cys
TTA	Leu	TCA	Ser	TAA	STOP	TGA	STOP
TTG	Leu	TCG	Ser	TAG	STOP	TGG	Trp
CTT	Leu	CCT	Pro	CAT	His	CGT	Arg
CTC	Leu	CCC	Pro	CAC	His	CGC	Arg
CTA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CTG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
ATT	Ile	ACT	Thr	AAT	Asn	AGT	Ser
ATC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
ATA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
ATG	Met*	ACG	Thr	AAG	Lys	AGG	Arg
GTT	Val	GCT	Ala	GAT	Asp	GGT	Gly
GTC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GTA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GTG	Val	GCG	Ala	GAG	Glu	GGG	Gly

Figure 2 Genetic code. Codons in black boxes indicate the stop or termination codons.

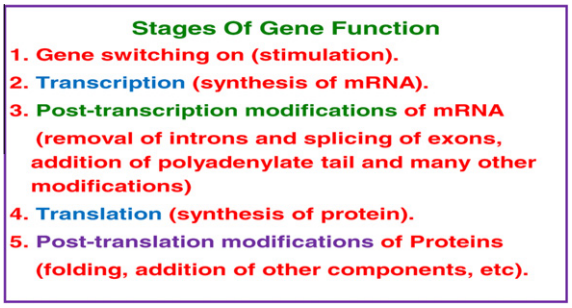


Figure 3 Stages of gene function.

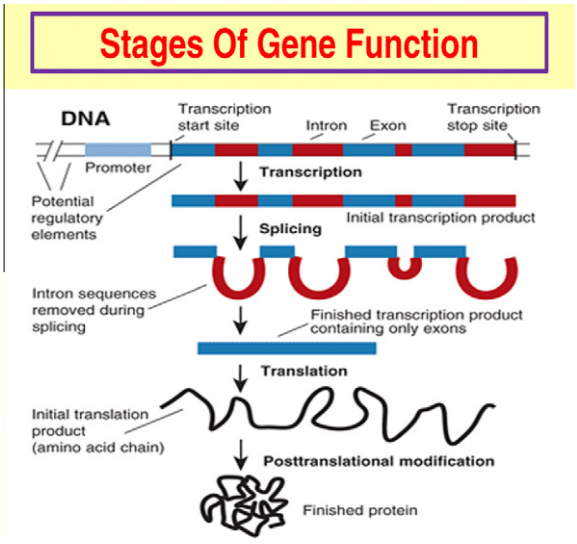


Figure 4 Stages of gene function [1].

turn the immature primary mRNA molecule into a final mature molecule capable of conducting its roles in protein synthesis. These modifications comprise many processes; viz removal of introns and splicing of exons, addition of a polyadenylate tail, capping and mRNA editing.

The process of gene transcription and synthesis of the messenger RNA comprises all parts of the gene with the exception of the promoter and termination regions. The resulting mRNA consists of bases complementary to bases of all the exons and introns of the gene. Since introns do not participate in protein synthesis except under certain conditions for specific genes, they must be removed from the primary mRNA in order to get the exact copy of the molecule carrying the exact information needed to synthesize the gene product. Introns are removed, trimmed or excised from the primary mRNA molecule followed by joining of, or splicing, the remaining exons to reconstruct the mRNA. This step, involving removal of introns and splicing of exons, is critical to proper gene function since it guarantees the synthesis of a protein with a specific number of amino acids arranged in a specific sequence, identical to the proper template of the protein as dictated by the genetic information contained within the gene. If incomplete excision of introns happens, a longer protein will be synthesized. Such proteins are usually unstable and easily degradable in the cytoplasm. Conversely, if axons are erroneously involved in this excision process, a shorter protein will be

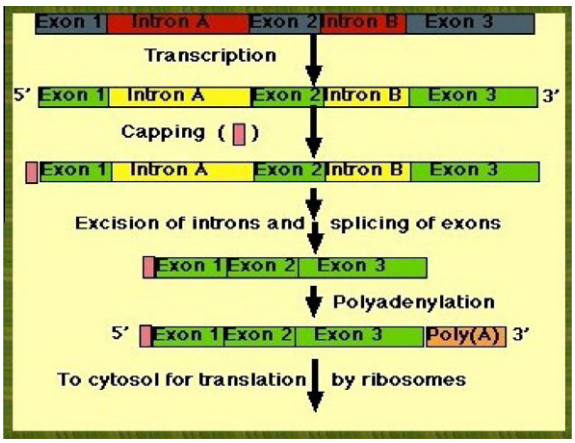


Figure 5 Stages of gene function (users.rcn.com/.../T/Transcription.html).

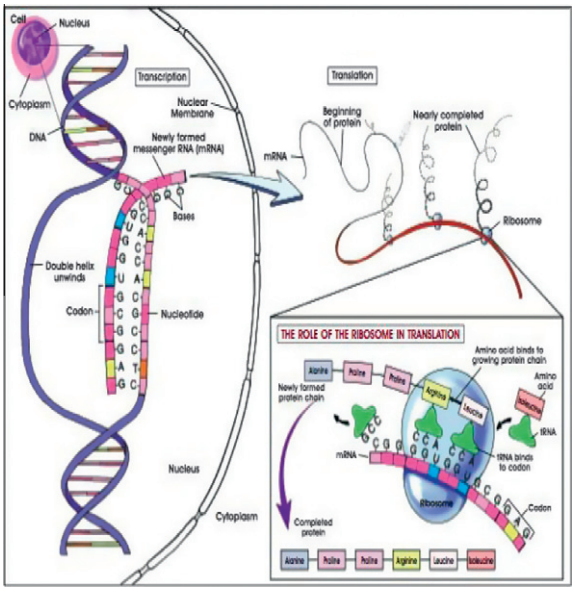


Figure 6 Translation and protein synthesis (bookbuilder.cast.org).

produced. According to the site and role of the missing amino acids in the protein molecule, a defective protein might be produced. In both of these instances, deficiency of protein or synthesis of defective protein might result, leading to pathogenesis and development of genetic diseases (Figs. 4 and 5).

The primary mRNA has to undergo other structural modifications necessary for conducting its mission. One of these modifications comprises addition of a long tail of a large number, 100–250, of adenine nucleotides to its 3′ end. This process of addition of a polyadenylate tail enables the mRNA to leave the nucleus through its transfer via the nuclear pores. It also stabilizes the mRNA molecule, protects it against degradation before its translation and controls its rate of degradation after completing its role in protein synthesis [3].

A third important modification of primary mRNA involves protective capping, or the addition of a methyl guanosine molecule to the 5′ end of the molecule to confer upon it resistance to degradation by 5′ exonucleases enzymes. Capping probably

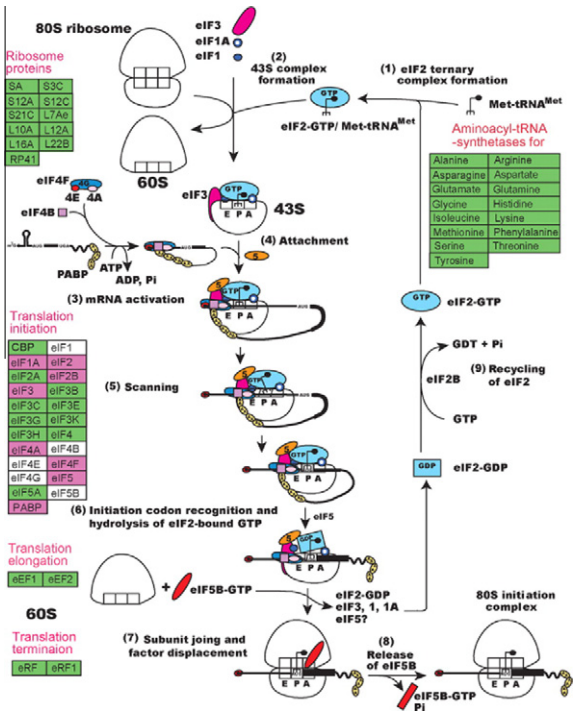


Figure 7 Translation and protein synthesis (molecular & cellular proteomics. mcponline.org).

has other functions; it may regulate export of the molecule from the nucleus, it may promote excision of the 5′ proximal intron and it may promote role of the molecule in translation. Failure of capping of mRNA results in premature degradation of the molecule and failure of protein synthesis [4].

An important post-transcription modification of primary mitochondrial mRNA in some protozoan species, sometimes called mRNA editing, can occur in response to certain mutational conditions and can be considered as one of the many anti-mutation mechanisms of the genome. RNA editing comprises a complex series of reactions aiming at repair of some point mutations, mostly frameshifts, of the molecule by a special subtype of small or microRNA (miRNA) called guide RNA (gRNA). These point mutations found in the mRNA, not in the gene, might occur during the transcription process and are referred to as secondary mutations [5].

The above mentioned post-transcription modifications of primary mRNA are necessary to render it final, or mature, molecule before its participation in the process of protein synthesis.

5. Translation

Translation, the fourth stage of structural gene function, entails the different interactive steps and the multiple cooperative processes necessary to synthesize proteins coded by genes. The name comes from the resemblance of the process to translation, i.e. gene language represented by codons or bases is translated to protein language represented by amino acids. During translation, proteins are synthesized on ribosomes by linking amino acids together in the specific linear order stipulated by the sequence of codons in an mRNA. Translation can be divided into four consecutive stages: initiation, elongation, termination, and recycling. In initiation, the ribosome is assembled at the initiation codon in the mRNA with a methionyl initiator tRNA bound (presumably) in its peptidyl (P) site. In elongation, aminoacyl tRNAs enter the acceptor (A) site where decoding takes place. If they are the correct (cognate) tRNA, the ribosome catalyzes the formation of a peptide bond. After the tRNAs and mRNA are translocated such that the next codon is moved into the A site, the process is repeated. Termination takes place when a stop codon is encountered and the finished peptide is released from the ribosome. In the final stage, recycling, the ribosomal subunits are dissociated, releasing the mRNA and deacylated tRNA and setting the stage for another round of initiation [4].

The above outline of the stages of translation describes the fundamental events in the process that occur throughout all forms of life. Translation is quite complex, and many aspects of its exact dynamics are still vague. In addition to the four major components of the translation process; the ribosomes, mRNA, tRNA and the amino acids, each stage of the process involves the participation of tens of different factors necessary

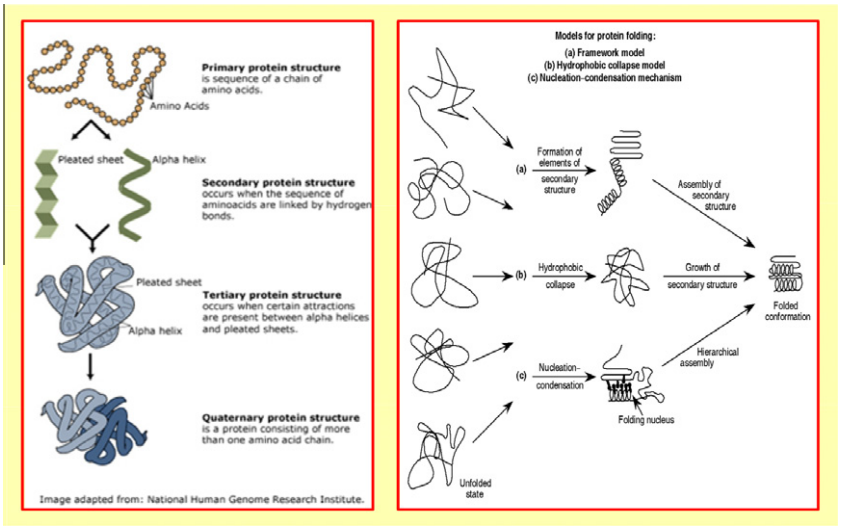


Figure 8 Post-translation modifications of proteins.

for mediating and conducting its consecutive steps (Figs. 6 and 7).

6. Post-translation modifications

Following translation and synthesis, the majority of freshly synthesized proteins have to undergo multiple consecutive conformational and structural alterations before they can perform their destined biological functions inside the cell or outside it. These changes are referred to as post-translation modifications. Examples of such modifications include conformational folding of straight polypeptide chains, proteolytic cleavage, glycosylation, acetylation, fatty acylation, and disulfide bond formation [6].

A large number of genetic diseases result from defective or deficient post-translation modifications because these modifications are critical to preparing the protein for its proper functioning. For instance, folding of a straight polypeptide chain is critical to proper function of many structural proteins, e.g. alpha-1-antitrypsin, and also for catalytic proteins destined to work as enzymes for many purposes, e.g. to allow conjugation with cofactors or prosthetic groups (Fig. 8).

Most proteins that are secreted, or bound to the plasma membrane, are modified by glycosylation or addition of a carbohydrate residue. This modification confers unique functional activities on these proteins, and several transcription factors and RNA polymerase II have been shown to be modified by such glycosylation. Proteins with an attached carbohydrate residue, glycoproteins, play critical diverse physiological roles in cellular functions like cellular adhesion and communications, recognition by the immune system and regulation of extra-cellular matrix homeostasis.

Hydroxylation represents an important post-translation modification of many important proteins, notably collagens that must be hydroxylated at their proline and lysine amino acids. Addition of sulfate group, sulfation, at the tyrosine amino acid residues of some proteins, or another important post-translation modification is necessary for proper function of many proteins, e.g. fibrinogen and gastrin [6].

Appendix A. MCQs medical genetics

Select only one best answer for each question:

1. Lisch nodules are pathognomonic clinical findings in the following diseases:

A. Watson syndrome
B. Sturge–Weber syndrome
C. Gardner syndrome
D. Neurofibromatosis Type I
E. A&D

2. Cataract is a frequent feature of all of the following conditions EXCEPT:

A. Congenital rubella syndrome
B. Chondrodysplasia punctata
C. Seckel syndrome
D. Lowe syndrome
E. Hallermann–Streiff syndrome

3. Dominant negative mutation effects are seen in:

A. Huntington disease
B. Cystic fibrosis
C. Retinoblastoma
D. Marfan syndrome
E. None of the above

4. Immune deficiency in adenosine deaminase deficiency is due to:

A. Shortened life span of T-cells
B. Shortened life span of B-cells
C. Defective immunoglobulin production
D. Combined T-cells and B-cells dysfunction
E. All of the above

5. Excess urinary excretion of keratan sulfate should suggest a diagnosis of:

A. GM_1 gangliosidosis
B. Morquio syndrome
C. Hurler syndrome
D. Ehler Danlos syndrome
E. Cutis laxa

6. Hyperglycinemia should suggest a diagnosis of:

A. Connective tissue disorder
B. Organic acid disorder
C. Mitochondrial encephalomyopathy
D. All of the above
E. None of the above

7. Pseudodominant inheritance refers to:

A. Apparent dominant (parent to child) transmission of a known multifactorial disorder
B. A. D. Apparent dominant (parent to child) transmission of a known chromosomal disorder
C. A. D. Apparent dominant (parent to child) transmission of a known microdeletion disorder
D. Apparent dominant (parent to child) transmission of a known autosomal recessive disorder
E. All of the above

8. Triplet repeat expansion disorders include the following:

A. Pseudoachondroplasia, Oculopharyngeal muscular dystrophy and Cleidocranial dysplasia
B. Myotonic dystrophy, Dentatorubral atrophy and polysyndactyly
C. Friedreich ataxia, fragile X syndrome and Myotonic dystrophy Type I
D. Friedreich ataxia, fragile X syndrome and Myotonic dystrophy Type II
E. All of the above

9. Progeria (Hutchinson–Gilford syndrome) is pathogenetically categorized as a:

A. Chanellopathy
B. Laminopathy

C. DNA repair defect
D. Signal transduction defect
E. Post-transcription defect

10. The p53 gene and p53 protein have the following roles in the cell:

A. Arrest of division of chromosomally damaged cells till they are repaired
B. Initiation of apoptosis of cells damaged beyond repair
C. Suppression of transformation of proto-oncogenes to oncogenes
D. All of the above
E. None of the above

11. genetic diseases that can present with hematuria include:

A. Systemic lupus erythematosis, IgA nephropathy (Berger disease) and Lesch–Nyhan syndrome
B. Hyperoxaluria, hyperphosphatasia and methylmalonic aciduria
C. Alport syndrome, sickle cell trait and Wegener granulomatosis
D. Polycystic kidney disease, Hyperoxaluria and methylpropionic acidemia
E. Alport syndrome, homocystinuria and Wegener granulomatosis

12. Inherited pancytopenia syndromes are seen in all of the following EXCEPT:

A. Shwachman–Diamond syndrome
B. Down syndrome
C. Pearson syndrome
D. Scleroderma
E. Noonan syndrome

13. Genetic syndromes associated with localized hypopigmentation include:

A.Waardenburg syndrome
B. Piebaldism
C. Tuberous sclerosis
D. A&B
E. A&B&C

14. Genetic disorders of phagocyte function include all of the following except:

A.Familial Mediterranean fever
B. Chédiak–Higashi syndrome
C. Inflammatory bowel disease
D. Hyperimmunoglobulin E syndrome
E. Chronic granulomatous disease

15. Treatment of hyperammonemia due to urea cycle defects include the following EXCEPT:

A.Peritoneal or hemodialysis
B.Lactulose
C.Sodium bicarbonate
D.Nitrogen scavenger drugs
E.Provision of high calories as carbohydrates and fats

Model answers

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

References

[1] Pierce Benjamin A. Genetics. A conceptual approach. 2nd ed. Gordonsville, VA, USA: W.H. Freeman & Company; 2005.
[2] Watson James D et al. Molecular biology of the gene. 5th ed. Menlo Park, CA, USA: Benjamin Cummings; 2004.
[3] Pasternak JJ. An introduction to human molecular genetics. 2nd ed. Hoboken, NJ, USA: Wiley-Liss, John Wiley & Sons, Inc.; 2005.
[4] Kapp LD, Lorsch JR. The molecular mechanics of eukaryotic translation. Ann Rev Biochem 2004;73(1):657–704.
[5] Ochsenreiter T, Cipriano M, Hajduk SL. KISS: the kinetoplastid RNA editing sequence search tool. RNA 2007;13(1):1–4.
[6] Rédei GP. Encyclopedia of genetics, genomics, proteomics and informatics. 3rd ed. New York, USA: Springer publishing company; 2008.