The Egyptian Journal of Medical Human Genetics (2013) **14**, 117–122

Ain Shams University

The Egyptian Journal of Medical Human Genetics

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www.sciencedirect.com

EDUCATIONAL CORNER OF THE ISSUE

Basic concepts of medical genetics, pathogenetics, Part 2

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Received 13 August 2012; accepted 31 August 2012
Available online 23 October 2012

1. Pathological mechanisms of mutation

1.1. Molecular mechanisms of point mutations

Point mutations refer to mutational events that involve one single base of the gene irrespective of the size of the gene. Lethal genetic diseases can be caused by single point mutations, even in very large genes. A well known example is Duchenne myopathy due to single point mutations of the dystrophin gene which is the largest human gene composed of 2.4 million bases. Sickle cell anemia is another example of a drastic genetic disease resulting from a single point mutation of the beta globin gene. Point mutations account for nearly 70% of currently defined human single gene disorders [1].

Molecular mechanisms of point mutation comprise a wide spectrum of alterations at the molecular level of the genetic material (Fig. 1). These mechanisms include replacement of one base (nucleotide) of the gene by another base, deletion, or loss, of one base of the gene, addition of one base to the gene or change in the structure of one base of the gene, e.g. by methylation, acetylation etc. Replacement of one base by another base may not affect the function of the gene or, on the other hand, can have drastic effects on gene function according to the type and consequences of the change. If one base of a functional codon is replaced by another base changing the codon to another codon specifying the same amino acid, due to degeneracy of the genetic code, then no change in structure of the protein coded by the gene happens, and no pathological alterations happen. This type of point mutation is called same-sense mutation since no change in protein structure happens. If the resulting new codon specifies a different amino acid a missense mutation results, the effects of which depend on the role played by the new amino acid in protein functioning. If the new amino acid has an important role within a critical functional domain of the protein, then pathophysiological alteration(s) of the function(s) of the protein is expected and defective function leading to pathogenesis of a genetic defect might ensue. If base replacement results in the formation of a new stop or termination codon, a status termed non-sense mutation, the resulting alterations depend on many factors. If the mutation happens at the beginning of the coding part of the gene, most of the protein coded by the gene will not be translated from this point on. A short, or truncated, mostly non-functional protein will be synthesized and marked deterioration of gene function might result. If the mutation happens at or near the end of the coding part of the gene, most of the protein coded by the gene will be translated and less, or no change, of gene function might result. In both situations, the resulting pathogenetic alterations depend on the physiological role(s) played by the missing domain(s) of the protein. If these roles are important in mediating functions of vital metabolic networks in the cell, then genetic defects will happen and pathogenesis of a genetic disorder might ensue.

Deletion or addition of one base within the gene will result in shifting of the reading frame of the newly formed codons. This type of point mutation is called frame-shift mutation. The resulting effects may lead to the formation of new same-sense, missense or stop termination codons with ultimate consequences similar to the results of the similar aforementioned mechanisms. These same rules apply for mutational events involving the addition or deletion of two bases. If three bases are added or deleted, a whole new codon will be added or

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Peer review under responsibility of Ain Shams University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejmhg.2012.08.009

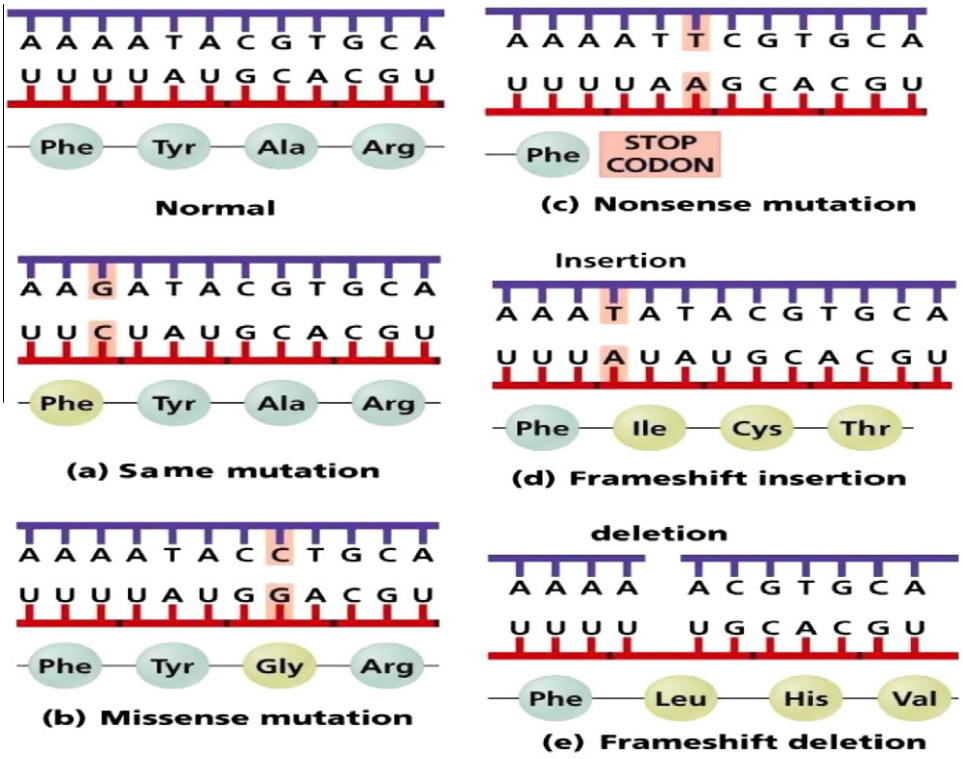

Figure 1 Molecular mechanisms of point mutation.

removed, respectively. Whereas addition or deletion of one codon to a functional exon of the gene might result in a wide spectrum of alterations as previously explained, whole codon addition or deletion within non-coding parts of the gene, introns, has no effect on translated protein or on gene function [2].

Change in the structure of one base of the gene, e.g. methylation of cytosine, can affect gene transcription through several different mechanisms. Each cell has a specific methylation pattern necessary for normal cell differentiation during development. Changes in this pattern by mutations of regulatory genes controlling its timing and its magnitude can have marked deteriorating effects on the cell during differentiation. This type of mutation must not be confused with epigenetic mutations that involve structural changes in the chromatin or the DNA-associated proteins rather than the DNA itself [3].

1.2. Molecular mechanisms of small mutations

Small mutations are arbitrarily classified so as to comprise structural changes involving more than one base, part of a gene, a whole gene or few genes. They span a wide spectrum of structural genetic changes involving addition or removal of two bases leading to frame shift mutations, addition or removal of one or more codons, single or multiple exon deletion or duplication, single or multiple intron deletion or duplication, single or multiple gene deletion or duplication and transposon-induced mutations.

The pathophysiological consequences of these mutations depend on the resulting changes in either the genetic regulatory networks or the metabolic networks of the cell secondary to deficient and/or defective synthesis of the gene product. The resulting deterioration of gene function leading to pathogenesis of a genetic disorder correlates with the extent of deficiency of the gene product, whether due to actual deficiency of the protein or regulatory small RNA coded by the gene due to suppression of gene function and inability to synthesize the gene product, or to relative or absolute deficiency of the function of a faulty synthesized gene product. Deletion of large portions of a gene, multiple exon deletions for instance, result in the synthesis of grossly defective protein lacking most or much of its domains needed to mediate its destined physiological roles causing marked pathophysiological deteriorations in the functioning metabolic networks dependent on these roles, thus predisposing to development of genetic disorders.

Small mutations of bases involved in splisosome mechanisms mediating intron excision and splicing of remaining exons, as part of the post-transcription modifications of mRNA, can have marked effects on the translation efficiency of the final mRNA and is a well-known mutational mechanism that underlies the pathogenesis of many common and serious genetic diseases (Fig. 2). These splice site mutations may result in over excision of parts of adjacent exons and synthesis of shorter polypeptide chains. If the missing amino acids coded by the over excised parts are important for mediating protein function or maintaining its structural integrity, then pathophysiological alterations and pathogenesis of disease might be expected. On the other hand, if splice site mutations result in skipping of an intron, part of an intron, a whole intron or multiple introns from excision, the resulting translated protein might be large enough to be unstable and easily degradable, or its structural configuration might be altered in such a way that

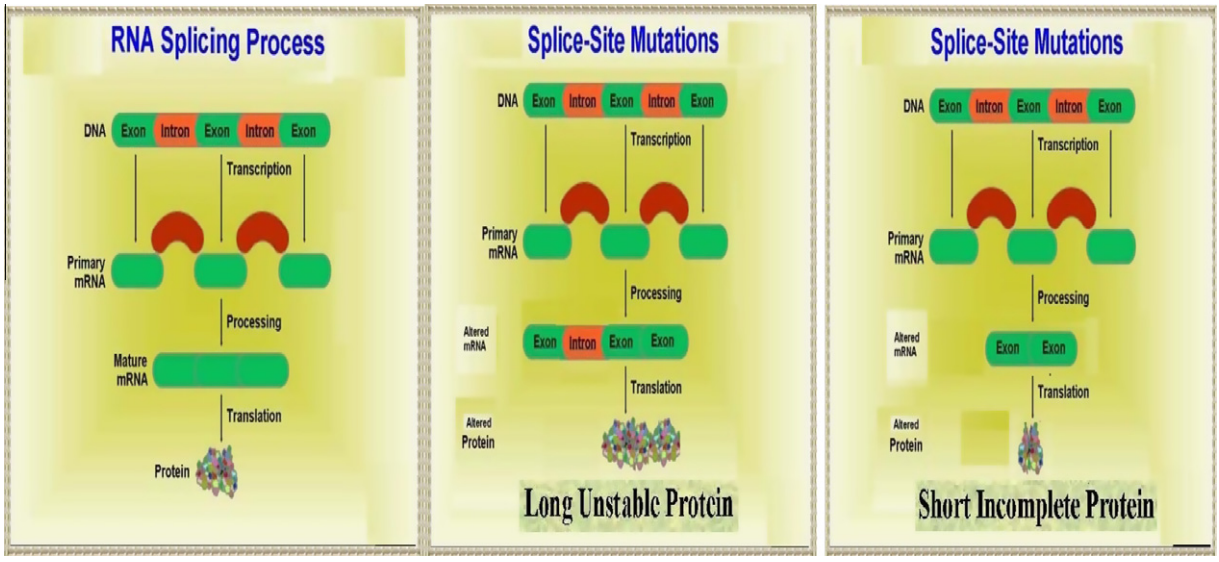

Figure 2 Splice site mutations.

its functional domains are no more accessible to each other or to other components, e.g. substrates or intermediary metabolites, needed for mediating its physiological functions, and a pathogenetic defect results [4].

1.3. Molecular mechanisms of gross mutations

Gross mutations are mutations that involve large portions of the genetic material. Chromosomal aberrations represent the prototype of this type of mutation, since even the smallest functional portion of a chromosome may consist of tens to hundreds of genes. Chromosomal abnormalities include many types of mutations which may involve the number of chromosomes, numerical chromosomal abnormalities, or the structure of chromosomes, structural chromosomal abnormalities. These abnormalities might also be classified into autosomal anomalies if they affect the autosomes (chromosomes 1–22) and sex chromosomal anomalies if they involve the sex chromosomes (X and Y chromosomes) [1].

Chromosomal mutations	
Structural mutations	Numerical mutations
1. Deletion	1. Trisomy (47 chromosomes)
2. Translocation	2. Monosomy (45 chromosomes)
3. Insertion	3. Hypodiploidy (less than 46)
4. Ring chromosome formation	4. Hyperdiploidy (more than 46)
5. Dicentric chromosome formation	5. Triploidy (3N: 69 chromosomes)
6. Chromosome gaps and breaks	6. Tetraploidy (4N: 92 chromosomes)

Both categories of chromosomal abnormalities comprise many different types of alterations in chromosome structure (deletion, translocation, inversion, ring chromosome formation, etc) and in chromosome number (monosomy, trisomy, hypodiploidy, hyperdiploidy, polyploidy, etc). Chromosome gaps and breaks represent mutations leading to interruption of the integrity of the chromosome DNA. They, probably, dispose to development of many other types of structural aberrations of chromosomes (Fig. 3).

The pathogenetic mechanisms involved in the pathogenesis of chromosomal aberrations are, still, mysterious and hardly understandable. They cannot be interpreted on molecular basis even for chromosome gaps and breaks in view of the complex structural assembly of the chromosome and its intimate integrity with the chromatin material. Gross regulatory defects of mechanisms controlling cell division, including the formation of the spindle and the timing of its action in synchronization with other biochemical and signal transduction effectors are held responsible for predisposing to non-disjunction and the development of chromosomal trisomies and chromosomal monosomies as well. Similar defective regulatory mechanisms might underlie the development of polyploidy conditions like triploidy and tetraploidy [5].

However, the regular and persistent occurrence at nearly constant incidence rates of well recognized and well defined genetic defects, including chromosomal aberrations, irrespective of ethnic, racial or environmental factors, indicates that these types of genetic changes or mutations might have, still unknown, deep rooted significant background in our genome. Disclosure of master genes and related genetic factors responsible for regulating both the stability and behavior of the genome as a whole will, surely, throw more light on factors underlying pathogenesis and development of chromosomal abnormalities.

1.4. Molecular mechanisms of genomic mutations

Genomic mutations refer to mutations involving the whole genome (either the 23 chromosomes haploid genome or the 46 chromosomes diploid genome). They comprise mutations of the whole chromosome set of the genome like triploidy (69 chromosomes genome) and tetraploidy (92 chromosomes genome). They, also, include mutational events leading to disturbed and/or defective expression of the whole genome functions. Genomic functional mutations reveal their

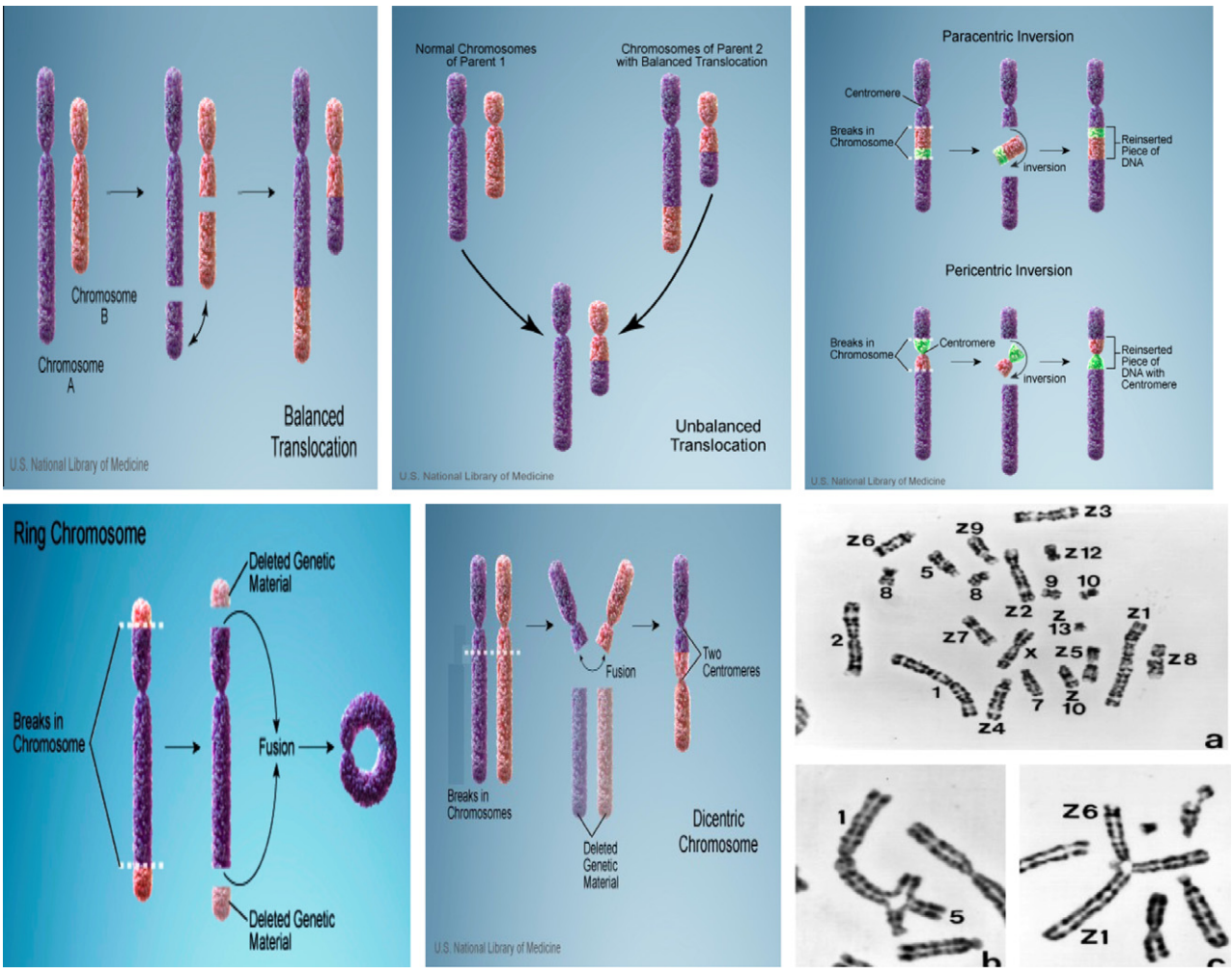

Figure 3 Different types of chromosomal aberrations, breaks and rearrangements.

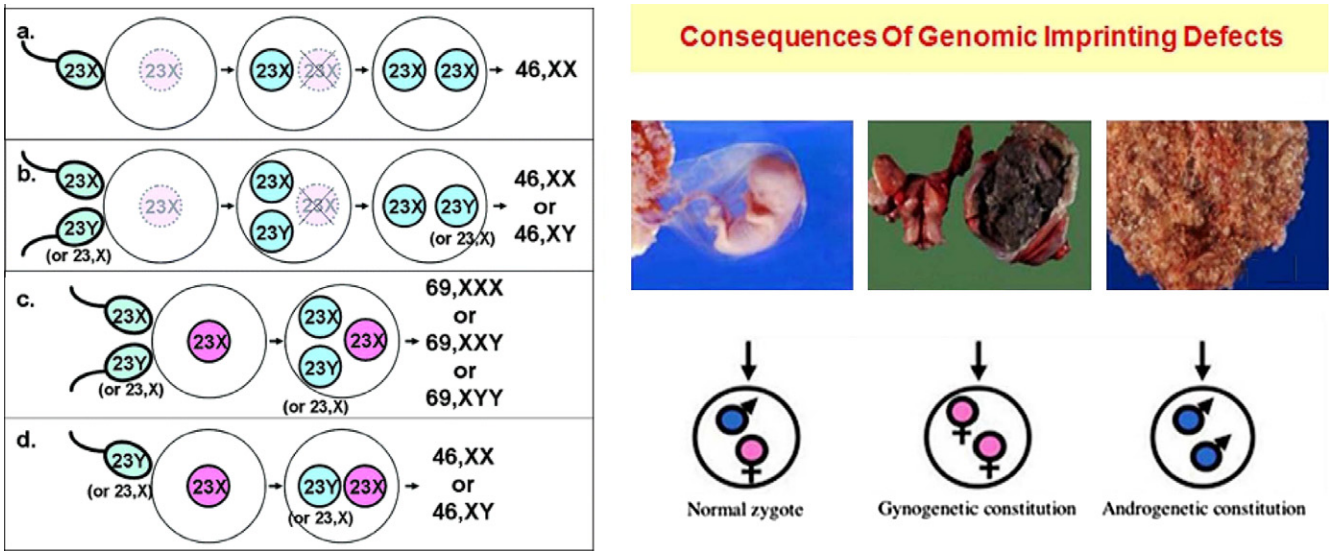

Figure 4 Some pathological consequences of genomic structural and functional mutations.

consequences in many phenotypes. In human, the development of vesicular or hydatidiform mole and the formation of dermoid cyst, instead of normal development of the zygote, represent obvious examples of genomic

functional mutations. Normally, during the first five days following fertilization and zygote formation, all cellular processes including cell growth, differentiation and division are controlled and mediated exclusively by the maternal genome of the ovum. The sperm genome begins its participation in these processes after these critical five days of post-fertilization period. Improper temporal programing of these genomic balances and interactions, e.g. due to genomic imprinting mutations, leads to disturbed genomic regulation of development and differentiation of the developing zygote, with drastic consequences leading to actual cessation and disturbed progress of normal development and differentiation. If the maternal genome fails to start functioning properly after fertilization or fails to maintain its genetic regulation of development over the critical immediate post-fertilization period, or if the paternal genome is prematurely induced to start its roles in genetic regulation of development and differentiation as a result of these genomic imprinting mutations, normal embryogenesis and/or fetal growth is brought to a standstill [2].

Genomic functional mutations might, also, be caused by other pathogenetic mechanisms, one of these abnormal mechanisms entails exclusive predominance of one parental genome in zygote formation and development. The diploid genome of the zygote may be formed from two maternal haploid genomes (46, XX) without any sperm genome, or from two paternal haploid sperm genomes (46,YY) without participation of any maternal genome. These abnormalities in chromosomal constitution of the zygote can be caused by many pathogenetic mutational events. Endoreduplication of one parental genome of the zygote with suppression, involution and disappearance of the other genome, or fertilization of the ovum by two sperm genomes with consequent disappearance of the ovum genome from the developing zygote can lead to pathogenesis of these genomic chromosomal abnormalities. A well-known wide spectrum of pathological embryonic and fetal malformations and abnormal conception products results from these genomic functional mutations (Fig. 4) [6].

Conflicts of interest

No conflicts of interest to declare.

Appendix A. Part II: MCQ

1. MCQs – Medical genetics

1.1. Select only the best one answer for each question

1- Which of the following diagnostic techniques is of no value in the diagnosis of neural tube defects:

A- Amniocentesis
B- Chorionic villus sampling (CVS)
C- Maternal serum screening
D- Ultrasonography
E- None of the above

2- Which of the following conditions is NOT caused by a mutation in FGFR3:

A- Achondroplasia
B- Crouzon syndrome
C- Thanatophoric dysplasia
D- Waardenburg syndrome
E- Hypochondroplasia

3- Marfan syndrome is caused by mutations in the gene which encodes:

A- Collagen
B- Ankyrin
C- Elastin
D- Spectrin
E- Fibrillin

4- Ehlers–Danlos syndrome is caused by mutations in the gene which encodes:

A- Collagen
B- Ankyrin
C- Elastin
D- Spectrin
E- Fibrillin

5- 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

6- 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

7- Precautionary measures during Valproic acid treatment of seizures INCLUDE:

A- Close monitoring of liver functions
B- Close monitoring of serum ammonia level
C- Close monitoring of serum carnitine level
D- Periodic assay of serum drug level
E- All of the above

8- Reliable diagnosis of the various types of Ehler–Danlos syndrome can be attained via:

A- Molecular testing by mutation analysis
B- Biochemical study of collagen synthesis defects
C- Assay of urinary analyte
D- A, B and C
E- A and B

9- The following statements about I-cell disease are true EXCEPT:

A- Psychomotor retardation is a major clinical manifestation
B- Bone marrow transplantation offers radical cure of affected children
C- The commonest causes of death are pneumonia and/or congestive heart failure
D- Linear growth decelerates during the first year of life and ceases by age of 2 years
E- There is trafficking defect of the synthesized enzyme to the lysosome

10- 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

11- Genetic hypertriglyceridemias can endanger life because of:

A- Biliary cirrhosis
B- Renal failure secondary to renal tubular dysfunction
C- Recurrent episodes of pancreatitis
D- Cerebral edema
E- Pulmonary fibrosis

12- Hypoglycemia is a common manifestation of the following diseases EXCEPT:

A- Type O glycogen storage disease
B- Fatty acid oxidation defects
C- Galactosemia
D- Fructosemia
E- Maple syrup urine disease

13- Each of the following is compatible with diagnosis of a mitochondrial disorder EXCEPT:

A- Encephalopathy
B- Myopathy
C- Skin hypopigmentation
D- Lactic acidosis
E- Renal dysfunction

14- Management of Turner syndrome patients include all of the following EXCEPT:

A- Growth hormone supplementation
B- Ovarian hormones supplementation
C- Calcium supplementation
D- Omega 3 fatty acids supplementation
E- Regular checkup for gonadal malignancies

15- Diagnostic features of Homocystinuria include none of the following EXCEPT:

A- Persistent lactic acidosis
B- Truncal obesity
C- Brachydactyly
D- Delayed bone age
E- Visual defects

Model answers.

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

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