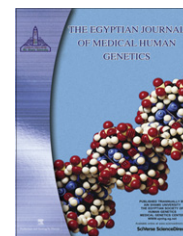




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EDUCATIONAL CORNER OF THE ISSUE

Basic concepts of medical genetics, pathogenetics: Part 1

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1. Pathogenetics

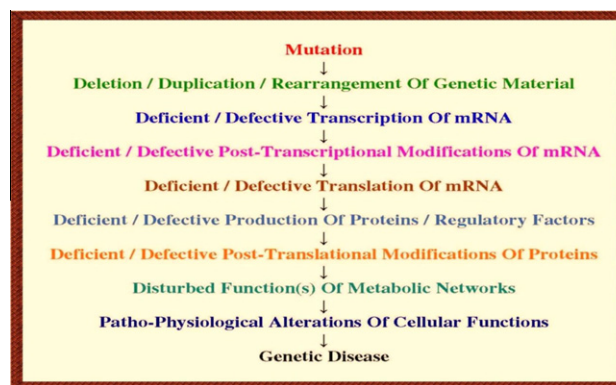
The term pathogenetics has been coined to encompass the various and different mechanisms involved in pathogenesis of genetic diseases. It comprises the study of mutations, the study of mutagens, the study of the different pathogenetic mechanisms that result from disordered gene functions secondary to the change of gene structure, the study of the pathophysiological alterations in cellular functions secondary to the ensuing disturbances of the metabolic-regulatory networks that mediate and control these functions and, finally, the study of pathogenesis of genetic diseases.

2. Pathogenesis of genetic diseases

Genetic diseases are caused by mutations, or structural changes of the genetic material at any of its organizational levels. Mutations cause disturbances and alterations of the structure and/or function of the genetic material, leading ultimately to one or more of the following consequences:

1. Deletion, or loss, of part of a gene, one or many genes, part of a chromosome, one or more chromosomes, one or more of mitochondrial genes, or even a whole genome.
2. Duplication/rearrangement of the genetic material.
3. Deficient/defective transcription of mRNA.
4. Deficient/defective post-transcriptional modifications of mRNA.

5. Deficient/defective translation of mRNA leading to deficient/defective production of gene products.
6. Deficient/defective post-translational modifications of proteins.
7. Deficient/defective synthesis of genetic regulatory factors. These include transcription nucleoproteins, transcription factors, microRNA, etc [1].



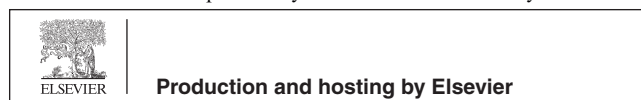
Irrespective of the site, type, nature or magnitude of the mutational event(s) that drastically affect the genetic material, the resultant alterations in gene function(s) trigger many disturbances in one or more of the cellular metabolic regulatory networks mediated by the deficient/defective gene products, thus leading to a wide and varied spectrum of pathophysiological changes in cellular functions leading, ultimately, to development of genetic diseases.

The specific pathognomonic phenotype that characterizes each genetic disease is primarily determined by the spectrum of pathophysiological changes in affected subjects. These, in turn, are determined by the spectrum of the mutation-induced damage to the genetic material in affected patients.

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3. Mutation

Mutation entails any uncoded or unprogramed permanent structural alteration of the genetic material at any of its organizational levels. These levels comprise a spectrum beginning with single nucleotide or a part of the nucleotide (base, sugar, phosphate), DNA, RNA, genes, chromosomes, mitochondrial DNA (mtDNA) up to the whole genome.

The effects of mutations differ widely according to many factors. These factors include the nature and target of the mutagen, the timing and magnitude of the resulting damage, and the balance between synergistic effects and anti-mutation mechanisms of the genetic material.

Mutations may occur without an identifiable cause and are termed spontaneous mutations, or they may occur secondary to exposure to a known cause, and are referred to as induced mutations. Factors that can induce mutations in the genetic material are called mutagens [2].

4. Classification of mutagens

- A. According to their nature, mutagens are classified into three main categories:
1. Chemical mutagens: these compounds are innumerable in the environment and include, for example, organic compounds, asbestos, insecticides, herbicides, heavy metals, etc.
 2. Physical mutagens: these include particulate radiations like X ray, alpha particles, UV waves at 2800 Å wavelength, solar radiation, thermal and mechanical agitation of nucleic acids.
 3. Biological mutagens: these include living microorganisms like some viruses (cytomegalovirus, rubella virus and herpes virus) and toxoplasma gondii.
- B. According to their pathogenetic effects, mutagens are classified into four main categories:
1. Non-specific mutagens.
 2. Carcinogens are mutagens that induce malignant transformations in affected cells.
 3. Clastogens are mutagenic agents that can induce chromosome breaks in affected cells.
 4. Teratogens are mutagens that cause congenital malformations in exposed fetuses.

Mutagens: types, effects and examples

Mutagens	Effects	Examples
Carcinogens	Carcinogenesis and tumor formation	Chemical: Aflatoxins Biological: Retroviruses Physical: X-ray irradiation
Clastogens	Chromosome breaks, deletions, rearrangements	Chemical: Bleomycin Biological: HIV virus Physical: UV waves
Teratogens	Congenital malformations	Chemical: Valproate Biological: <i>Toxoplasma gondii</i> Physical: X-ray irradiation
Non-specific mutagens	Non-specific damage to the genetic material	Chemical: Innumerable types Physical: X-ray irradiation Biological: Toxoplasma, Viruses

Classification of mutation

1. Induced versus spontaneous mutation
2. Nuclear versus mitochondrial mutation
3. Somatic versus germinal mutation
4. Static versus dynamic mutation
5. Pathological versus non-pathological mutation
6. Point, small, gross and genomic mutation
7. Base, sugar, phosphate group mutation.
8. Persistent versus reversible mutation.

4.1. Induced and spontaneous mutations

Induced mutations are structural alterations of the genetic material that occur due to exposure to the effects of any of the known mutagens. Spontaneous mutations, on the other hand, happen, probably, on regular basis because of the intrinsic nature of the genome. For instance, insertional mutations caused by spontaneous or programmed movement of the transposons represent a major source of spontaneous mutations. Tautomerism of bases of the DNA also account for a considerable fraction of spontaneous mutations of the genetic material.

4.2. Nuclear and mitochondrial mutations

Nuclear mutations are mutations that affect nuclear genes carried on the chromosomes. Single gene disorders result from nuclear mutations that affect one or both genes of these disorders. Mitochondrial mutations affect genes of the mitochondria. Due to the presence of multiple copies, tens to thousands, of each mitochondrial gene inside each mitochondrion, pathogenesis of mitochondrial disorders requires the affection of a large fraction, nearly 80%, of the copies of the specific disease gene responsible for the mitochondrial disorder by the mutation.

5. Somatic and germinal mutations

Somatic mutations are mutations that affect the genome of somatic cells. The consequences of these mutations span a wide spectrum of pathological effects that include immediate or gradual cell death, progressive failure of cell functions, induction of apoptosis and malignant transformation. Conversely, germinal mutations that affect germinal cells are characterized by being heritable mutations. If the affected germ cell participates in fertilization and formation of the zygote, the mutation will be inherited leading to affection of the offspring.

6. Static and dynamic mutations

Static mutations are mutations that are transmitted as they are from an affected parent to an offspring. The mutation in the offspring is identical to that of the parent. Dynamic mutations, on the contrary, are mutagenic changes that increase in magnitude upon transmission from a carrier parent to his offspring. Triplet repeat expansion mutations that account for a large number of genetic diseases like fragile X mental retardation, Friedreich ataxia, Huntington's disease and many others, represent an obvious example of dynamic mutations of the human genome.

7. Pathological and non-pathological mutations

Pathological mutations are mutations that cause genetic disorders secondary to their damaging effects on structural, regulatory or master genes involved in the synthesis of proteins, transcription of non-coding RNA subtypes and the regulation of various vital cellular functions. Many mutations, however, do not result in pathological consequences to affected cells due to many factors, e.g. they might affect the non-genic parts of DNA, same-sense point mutations and mutations that are corrected by DNA and/or RNA repair systems. Miss-sense mutations of structural genes that affect amino acids in non-critical domains of the protein do not result in pathophysiological alterations or functional deterioration, rather they might result in non-pathological changes of other aspects of the protein, e.g., its molecular weight or its electrophoretic mobility [3].

8. Point, small, gross and genomic mutations

Mutations are arbitrarily classified according to the magnitude of the mutational damage into point, small, gross and genomic mutations. Point mutations refer to mutation of one single base of the gene irrespective of the size of the gene. Small mutations involve larger mutations of many bases, one or more exons or introns and one or more genes. Gross mutations comprise chromosomal abnormalities where tens, or even hundreds, of genes are affected by deletion, inversion or translocation. Genomic mutations represent the extreme end of the spectrum of mutations where the whole genome undergoes mutational changes. Triploidy and tetraploidy represent rare examples of these genomic mutations. Also, aberrant development of vesicular moles and dermoid cysts represent clear examples of genomic mutations due to disordered imprinting of the whole haploid genome of the germinal cells following fertilization.

9. Base, sugar, phosphate mutations

Mutations, in general, refer to changes of the bases of the nucleic acids (A,G,C,T,U) and represent the commonest types of mutations of the genetic material. However, several kinds of mutations can affect the sugar portion of the nucleotide. Some physical and chemical mutagens can add an oxygen to the deoxyribose of DNA or remove an oxygen from the ribose of RNA or a whole deoxyribonucleotide might be substituted by a ribonucleotide. Such mutants with a ribonucleotide, instead of a deoxyribonucleotide, are usually silent but under abnormal conditions they might be attacked by ribonucleases leading to DNA breaks. Methylation of ribose of a coding nucleotide in mRNA may, also, lead to silencing or, even, to total suppression of translation.

Mutations that affect the phosphorus atom of the nucleotide can cause widespread detrimental effects on the integrity of the DNA strand. Irradiation turns ordinary phosphorus to radioactive phosphorus which, upon release of an electron, changes to non-radioactive sulfur and suffers a recoil in diameter leading to loss of its connection to the adjacent sugar. This results in multiple recoil breaks in the sugar-phosphate backbone of the DNA with ultimate breakage mutations of the nucleic acid.

10. Persistent and reversible mutations

Persistent mutations are mutations that cannot be corrected by the repair systems of the genome, get fixed in the affected portion of the genetic material and act as permanent structural alterations that can be transmitted, or inherited, from a carrier parent to an offspring. Reversible mutations, on the other hand, represent transitory programmed changes of the genetic material that mediate specific transient regulatory functions, e.g., base methylation for suppression of gene function when there is no need for more of the gene product. Reversible mutations also include mutations corrected by repair systems and reversible breakage and reformation of hydrogen bonds between bases of the DNA following thermal agitation of the molecule [4].

Conflicts of interest

No conflicts of interest to declare.

Appendix A. Part II: MCQ

K.1. MCQs – Medical genetics

Select only the best one answer for each question:

- Genetic counseling includes all of the following EXCEPT:
 - Recommendation of specific reproductive options
 - Assessment of the occurrence or recurrence risk
 - Discussion of the impact of the disease on the patient and family
 - Discussion of available therapies
 - Discussion of available genetic testing.
- A true statement regarding Noonan Syndrome is:
 - Is a chromosomal syndrome
 - Is an autosomal recessive disorder
 - Is called “male Turner” and only affect males
 - Aortic stenosis is the most common cardiac abnormality
 - Mutation in *PTPN11* gene is associated with 50% of the cases.
- A liver transplant may be effective in treating all of the following disorders EXCEPT:
 - Severe familial hypercholesterolemia
 - α -1 antitrypsin deficiency
 - Ornithine transcarbamylase (OTC) deficiency
 - Tyrosinemia type I
 - β -thalassemia major.
- Prenatal diagnosis of congenital hypothyroidism is possible through determining:
 - Maternal levels of free T4 and TSH
 - Amniotic fluid level of Reverse T3
 - Maternal levels of free T4 and Thyroglobulin
 - Fetal biparietal diameter
 - Frequency of fetal movement.

5. Large quantities of useful products can be produced through genetic engineering involving:
- Bacteria containing recombinant plasmids
 - Yeast carrying foreign genes
 - Transgenic plants
 - Mammals producing substances in their milk
 - All of the above.
6. The term imprinting indicates:
- Loss of heterozygosity
 - Suppression of one parental allele by the other allele
 - Downregulation of heterochromatin
 - Differential suppression of genes based on parental origin
 - Variable timely expression of clinical features.
7. Which of the following is NOT a component in treatment of Homocystinuria:
- Vitamin B6
 - Folic Acid
 - 3-Methyl Glycine
 - Vitamin B12
 - Antioxidants.
8. Peutz-Jeghers syndrome (PJS) is characterized by all of the following EXCEPT:
- Gastrointestinal polyposis and mucocutaneous pigmentation
 - Innate cellular immunodeficiency
 - Affected individuals are at increased risk of malignancies
 - Can be diagnosed both prenatally and postnatally by molecular testing
 - It is inherited in an autosomal dominant manner.
9. Chromosome breakage syndromes include None of the following EXCEPT:
- Nijmegen syndrome
 - Hashimoto's Thyroiditis
 - Shwachman syndrome
 - Rett syndrome
 - Smith-Lemli-Opitz syndrome.
10. Chediak-Higashi syndrome is characterized by the following features EXCEPT:
- Partial albinism
 - Nystagmus
 - Megakaryocyte inclusion granules
 - Recurrent infections
 - Increased susceptibility to develop malignant lymphoma.
11. Core signs/symptoms of Autism include the following EXCEPT:
- Disturbed Social interactions and relationships
 - Defective verbal and nonverbal communication
 - Enhanced feelings of fear of dangerous situations.
 - Limited interests in activities or play
 - Abnormal reactions to sensory stimuli.
12. New treatments of Phenylketonuria include the following EXCEPT:
- Neutral amino acids supplementation
 - Omega 3 & Omega 6 supplementation
 - Aspartame consumption instead of sugar
 - Biopterin cofactor
 - High-dose tyrosine supplementation.
13. Workup investigations for short stature include:
- Measuring serum level of insulin-like growth factor-1 (IGF-I)
 - Measuring serum levels of growth hormone (GH)
 - High resolution banding karyotype
 - Measuring serum level of insulin-like growth factor-binding protein-3 (IGFBP-3)
 - All of the above.
14. The following statements about Megaloblastic anemia are correct EXCEPT:
- It is due to impaired DNA synthesis
 - Its most common causes are cobalamin (vitamin B-12) and folate deficiencies
 - Repeated packed RBCs' transfusion therapy represents the mainstay of therapy
 - Reducing homocysteine levels improve vascular outcome in affected patients
 - Zollinger-Ellison syndrome can cause megaloblastosis and anemia.
15. The following statements about Pseudogenes are wrong EXCEPT:
- They represent evolutionary remnants of junk DNA
 - They are found exclusively in heterochromatin regions of chromosomes
 - They can take over the functions of imprinted genes
 - Some pseudogenes play a role in gene regulation and expression
 - They can be identified due to their rich content of A & T nucleotides.

Model answers.

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

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