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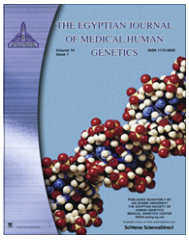

EDUCATIONAL CORNER OF THE ISSUE

Basic concepts of medical genetics, pathogenetics, part 3

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1. Pathogenetic mechanisms of genetic diseases

The genetic material controls life activities of the cell through regulating the synthesis of proteins which directly mediate these activities. Regulatory genes, in addition, control the transcription of many classes of small RNAs that have fundamental roles in direct and feed-back regulation of most aspects of the genetic material [1].

Mutations cause structural alterations of the genetic material. Depending on the site, nature, magnitude and effects of the mutational event as well as on the functions and importance of the mutated genes, pathogenetic mechanisms that result in **deficient synthesis of gene products**, **synthesis of defective gene products** or **disturbed regulation of cellular activities** will lead to the development of genetic disorders, secondary to the ensuing pathophysiological alterations of cellular functions.

Maintaining the **stability**, **integrity** and species-specific **identity** of the genome represents a prerequisite, not only for executing cell functions properly, but more fundamentally for the beginning, continuation and conservation of life. It is the preservation of the collaborative and integrated intimate relationship of these three aspects of the genome that represent the real kernel and true essence of existence of all forms of life. Many pathogenetic mechanisms that drastically affect genome stability and genome integrity have been defined. These particular groups of mutations constitute important detrimental events that act via different pathways, e.g. defective genetic repair mechanisms or the premature induction of apoptosis, leading ultimately to the loss of genome stability, integrity and induction of cell death. On molecular or cellular level, these mutations might be considered as **life-ending mutations**. These mutations might also act in a different way through the total loss of reproductive fitness and the disappearance of individual genomes from the gene pool of certain species [2].

The spectrum of pathogenetic mechanisms and the resulting pathophysiological disturbances that underlie the development of genetic disorders is quite wide in view of the complexity of the structural organization of the genome and the strict functional specialization that characterizes each of its components. Additionally, the obscure nature and unclear functions of many components of the genetic material, undoubtedly, conceal many, still unknown, pathogenetic mechanisms and hinder proper understanding of their exact pathways. It is hoped that the final completion of the human genome project might disclose the exact and complete structural organization of the human genome. However, a parallel human genome function project aiming at defining the complete functional spectrum of the genome seems to be an indispensable and imperative task in order to finalize the knowledge of our genetic material [3].

Currently defined pathogenetic mechanisms and pathophysiological alterations implicated in the pathogenesis of genetic disorders include the following:

1. Loss/damage/duplication/inactivation of nuclear genes
2. Mutation of mitochondrial genes (mitDNA)
3. Deficient/defective DNA replication/repair
4. Triplet repeat expansion disorders
5. Loss/acquisition/damage of chromosomes
6. Deficient transcription of mRNA
7. Transcription of defective mRNA
8. Deficient/defective post-transcription mRNA repair

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9. Deficient/defective post-transcription modifications of mRNA
10. Deficient translation of proteins
11. Translation of defective proteins
12. Deficient/defective post-translation modification of proteins
13. Deficient/defective post-translation repair of misfolded proteins
14. Deficient/defective post-translation targeting and trafficking of proteins
15. Deficient/defective regulation of cell growth
16. Deficient/defective regulation of cell division
17. Deficient/defective regulation of cell differentiation
18. Deficient/defective regulation of cell migration
19. Deficient/defective regulation of intercellular contact and cell movement
20. Deficient/defective apoptosis/selection repair
21. Deficient/defective regulation of cell architecture and cytoskeleton: e.g. ciliary dyskinesia disorders (bronchiectasis, dextrocardia and situs-inversus, hydronephrosis, hydrocephaly, male infertility and repeated abortions), hereditary spherocytosis, Wiskott-Aldrich syndrome and neural tube defects.
22. Imprinting disorders: genomic imprinting disorders, e.g. ovarian teratomas and hydatidiform moles, and genic imprinting diseases, e.g. Prader-Willi syndrome, Angelman syndrome, Silver-Russell syndrome and Beckwith-Wiedemann syndrome.
23. Deficient/defective regulation of cellular functions:
    a. Deficient/defective transport across cell membrane or membranes of cell organelles (transport defects)
    b. Deficient/defective transport across cell pores, nuclear pores or pores of cell organelles (chanellopathies)
    c. Deficient/defective secretion of gene products (protein/enzyme deficiency disorders)
    d. Deficient/defective excretion of metabolic waste products (storage disorders)
    e. Deficient/defective regulation of intra and inter network reactions and interactions: signal transduction disorders: e.g. neurodegeneration, diabetes mellitus, schizophrenia and Noonan syndrome.
    f. Deficient/defective positioning of structural proteins (cell cytoskeleton disorders)
    g. Deficient/defective regulation of intracellular trafficking.
    h. Deficient/defective production of cellular energy: oxidative-phosphorylation disorders.
    i. Ubiquitination/proteasome degradation defects: e.g. Friedreich ataxia, Huntington disease, Parkinson disease, Alzheimer disease, Angelman syndrome, motor neurone disease and immunodeficiency.
    j. Apoptosis defects: e.g. congenital malformations, autoimmune disorders, cancer and neurodegeneration [4,5].

2. Anti-mutation mechanisms of the human genome and human proteome

The human genome develops, persists and works in a hostile environment full of existing, and continuously generated, mutagens. Mutational events induced by external factors, which include physical, chemical and biological mutagens,

Table 1 Anti-mutation mechanisms of the human genome.

Anti-mutation mechanisms of the human genome	
Mechanism	Types & pathways & comments
1. Structural organization of the genome	1. Nuclear genome 2. Mitochondrial genome
2. Structural features of DNA	Complementary strand stores genetic information
3. Degeneracy of the genetic code	Multiple point mutations might occur without affecting synthesized protein
4. Nuclear localization of DNA	Physical protection of nuclear genome
5. DNA-associated proteins	1. Physical barriers 2. Biochemical buffers 3. Deactivating biomolecules 4. Modulation of charge transport 5. Limitation of DNA helix distortion
6. Replication proofreading system	Prophylactic pathway during DNA replication
7. Genetic repair systems	A. Nuclear DNA repair 1. Base excision repair 2. Nucleotide excision repair 3. Direct reversal repair 4. Mismatch repair 5. Recombination repair B. RNA repair/editing system Post-transcription repair/editing of some mRNA defects via guide RNA (gRNA)/editosome complex C. Mitochondrial DNA (mtDNA) repair
8. Protein repair systems	Correction of post-translation protein misfolding/aggregation by chaperones
9. Silencing of transposons by piwiRNA	Reduces transposon-induced mutations during development
10. Antioxidant enzyme systems	
11. Apoptosis	Prophylactic pathway against spread of mutations of heavily or lethally mutated genomes to daughter cells
12. Melatonin	Anti-clastogenic, anti-mutagenic, anti-carcinogenic and anti-oxidant compound.

have widespread detrimental effects on the stability and integrity of the **genome** as well as on the stability and integrity of the **proteome**. Additionally, further and considerable damage of the structural organization and functional capabilities of both the genome and the proteome regularly occurs on continuous and progressive basis due to the continuously generated burden of internal mutagens that result from the diverse metabolic activities of the exceedingly large number of metabolic networks of the cell. Unless a powerful and effective protective and repair system actively participates in protecting the genome and proteome of the cell against the deleterious effects of mutations, and in efficient repair of resulting damage, maintaining the stability and integrity of both of these bio-systems that constitute the framework of life activities within the cell would have been impossible [2].

The human genome is endowed with a spectacular multifaceted strong anti-mutation system responsible for maintaining stability and integrity of the genome and preserving its identity. It acts by protecting the genome from the detrimental effects of mutation and by repairing mutation-induced damage. Obviously, the balance between the pathological effects of mutation and the ability of the anti-mutation system to counteract and to reduce the consequences of these effects represents the main factor that determines the likelihood of having a mutation-induced genetic disease. The human anti-mutation system comprises both **innate** mechanisms common to, and shared by, all individuals, e.g. degeneracy of the genetic code, and **acquired** aspects determined by the inherited genetic background of each human being, e.g. DNA repair system [6].

The human **transcriptome**, being subjected to the same mutational events that can affect, alter and damage the DNA, seems to have efficient anti-mutation mechanisms to guard against occurrence of errors during RNA transcription and to correct and repair some post-transcription defects of mRNA that can cause errors during protein translation. A separate **RNA-proofreading system** seems to exist and it probably acts during transcription by relying on the sequence complementarity information or database stored within the complementary silent or non-transcribing strand of DNA. Depending on the sequence of the active strand to ensure accurate transcription might result in improper transcription if mismatch errors occur due to, e.g. polymerase dysfunction. This assumption might, partly, explain the still un-understandable behavior of gene function which involves, seemingly needless, indirect and energy consuming mechanisms by transcribing a complementary mRNA molecule, rather than an identical mRNA, that has to be decoded again by rRNA and tRNA in the ribosome during translation [Table 1].

Appendix A. Part II: MCQs

A.1. Choose the best answer

1- FISH stands for:
   a- fluorescent in situ hybridization
   b- first induced strand hybrid.
   c- F1 insertion segment homolog.
   d- flanking insertion sequence hybrid.
   e- fluorescent insertion segment hybrid

2- Lod score measures:
   a- the relatedness of two individuals.
   b- the length of genetic distances.
   c- how often double crossovers occur.
   d- the length of a linkage group.
   e- the likelihood of linkage between genes

3- Crossing over occurs during:
   a- interphase.
   b- prophase.
   c- metaphase.
   d- anaphase.
   e- telophase.

4- Inheritance of both chromosomes from the same parent is a condition called:
   a- displaced duplication
   b- uniparental disomy
   c- tandem duplication
   d- unbalanced polymorphism
   e- nondisjunction

5- Enzyme assay can be used to identify carriers of:
   a- Cystic fibrosis
   b- Fragile X syndrome
   c- Oculocutaneous albinism
   d- Tay-sachs disease
   e- β-thalssemia

6- Maternal serum level of alpha-fetoprotein (AFP) is lower than average in:
   a- Neural tube defects
   b- Exomphalos
   c- Down syndrome
   d- Twin preganancy
   e- Spina bifida

7- The risk for miscarriage associated with amniocentesis is approximately:
   a- 1 in 10
   b- 1 in 50
   c- 1 in 100–200
   d- 1 in 1000
   e- 1 in 10000

8- Which of the following karyotypes is NOT compatible with survival to birth:
   a- 47, XY, +13
   b- 47, XX, +18
   c- 47, XY, +21
   d- 47, XX, +16
   e- 48, XXY

9- The DiGeorge/Shprintzen syndrome is caused by a deletion in:
   a- chromosome 4
   b- chromosome 7
   c- chromosome 15
   d- chromosome 21
   e- chromosome 22

10- Which of the following is NOT a chromosome instability syndrome:
  a- Poikiloderma of Civatte
  b- Ataxia telangectasia
  c- Bloom syndrome
  d- Fanconi anemia
  e- Xeroderma pigmentosum

11- Polyploidy refers to:
  a- extra copies of a genes adjacent to each other on a chromosome
  b- complete extra sets of haploid genome
  c- chromosome which has replicated but not divided
  d- multiple ribosomes present on a single mRNA
  e- inversion which does not include the centromere

12- Choose the correct statement about the genetic code:
  a- includes 61 codons for amino acids and 3 stop codons
  b- is almost universal; exactly the same in most genetic systems
  c- consists of three bases per codon
  d- some amino acids are coded by multiple codons
  e- all of the above

13- X-chromosome inactivation:
  a- normally takes place in males but not females:
  b- is the cause of the Y chromosome being genetically inactive
  c- the same X chromosome is inactive in all of the cells of a female
  d- occurs in fruit flies but not in mammals
  e- results in genetically turning off one of the two X chromosomes in female mammals

14- Chromosome duplication denotes:
  a- reciprocal exchange between non-homologous chromosomes.
  b- loss of genes in part of a chromosome
  c- extra copies of genes on part of a chromosome
  d- a reversal of order of genes on a chromosome
  e- extra sets of chromosomes in an organism

15- Male to male transmission is a key feature of:
  a- Autosomal dominant inheritance
  b- Autosomal recessive inheritance
  c- X-linked dominant inheritance
  d- X-linked recessive inheritance
  e- None of the above

Answers:

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

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