Medical Genetics: An Overview

Mohammad Saad Zaghloul Salem*

Faculty of Medicine, Ain-Shams University, Cairo, Egypt

Abstract

Medical genetics is a branch of human genetics confined to studying structure and function of the genetic material in health and disease states of human beings. It comprises studying causes and mechanisms of pathogenesis of genetic disorders, clinical characterization of different types of these disorders and their modes of inheritance, study of diagnostic techniques used in their diagnosis and delineation of effective prophylactic and therapeutic measures resorted to in managing patients and carriers of these diseases. The wide spectrum of medical genetics includes six main fields: basic, clinical, diagnostic, prophylactic, therapeutic and applied genetics. The scopes of most of these fields are self-explanatory with few exceptions. Pathogenetics, a branch of basic genetics, implies the study of mutagens, mutations, pathogenetic mechanisms responsible for development of genetic diseases and anti-mutation mechanisms that protect the genome from the pathological consequences of these mechanisms. Formal genetics, another branch of basic genetics, is concerned with deducing and figuring out relevant genetic data from constructed figures that contain specific genetic information. These informative figures include, for instance, constructed family pedigrees, linkage maps and chromosomal maps. Applied genetics denotes use of knowledge of other fields of medical genetics in many significant applications like genetic counseling, fetal therapy and forensic genetics. Treatment of genetic disorders and prevention of their complications represent the main targets of therapeutic and prophylactic genetics, respectively. The importance of medical genetics resides in hopes of its ability to offer alleviating measures and curative therapies for dispreviledged patients with genetic diseases and, more importantly, to succeed in achieving radical preventive approaches of these diseases. This article is intended to offer a simple and concise overview of medical genetics including the various aspects of its different fields.

Spectrum of Medical Genetics

Medical genetics, as the name implies, is a branch of human genetics confined to, and concerned with, studying structure and function of the genetic material in relation to health and disease states of human beings. Within this context, it comprises the study of causes and mechanisms of pathogenesis of genetic disorders, clinical characterization of different types of these disorders and their modes of inheritance, study of diagnostic techniques used in their diagnosis and delineation of effective prophylactic and therapeutic measures resorted to in managing patients and carriers of these diseases. A plausible classification of the wide spectrum of the different fields of medical genetics, based on the subjects and aims of the different branches of each of these fields, recognizes six main fields of medical genetics: basic, clinical, diagnostic, prophylactic, therapeutic and applied genetics (Table 1).

Genetics and Life

All life activities in living cells, whether conducted on molecular level, e.g. electron transfer in oxidative phosphorylation reactions for production of ATP, on cellular level like cell division, on tissue level like muscle contraction or on whole organ level like hearing for instance, are mediated via very large numbers 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, product. Each metabolic network consists of a very large number, sometimes hundreds, of proteins, mostly enzymes, and other non-protein factors all acting cooperatively in stereotyped sequence to perform specific biochemical and physiological functions. In human cells, nearly 4100 (four thousand and one hundred) of these networks have been delineated [1]. The proteins which are constituents of and mediate these metabolic networks are synthesized in living cells under strict regulation of the genes contained within the cells. This intimate relationship between the genetic material and life activities is represented by the central dogma of molecular biology which states that while the sum total of the genetic material of the living cell, collectively referred to as the genome, defines the framework of all features and life processes in living cells, the sum total of the proteins produced and synthesized in the cell under strict control of the genome, collectively referred to as the proteome, are the actual and direct mediators of these life processes.

The Human Genome

The human genome, estimated to consist of 20000-25000 genes, is unequally divided into a major portion constituting more than 99.99% of its size, residing in the nucleus and structurally organized as chromosomes and is referred to as the nuclear genome. The remaining tiny portion exists as small circular molecules inside the mitochondria in the cytoplasm and is referred to as the mitochondrial genome (mtDNA). Albeit, much smaller portion of genomic DNA exists as a structure associated and attached to the inner surface of cell membrane and is referred to as cytoplasmic membrane associated DNA (cmDNA) [2]. The exact functional significance of this portion is, still, a matter of debate.

*Corresponding author: Mohammad SaadZaghloul Salem, Faculty of Medicine, Professor of Medical Genetics, Ain-Shams University, Cairo, Egypt, E-mail: mszsalem@hotmail.com

Basic Genetics	
1. Molecular genetics	10. Developmental genetics
2. Pathogenetics	11. Population genetics
3. Cytogenetics	12. Evolutionary genetics
4. Formal genetics	13. Comparative genetics
5. Biochemical genetics	14. Experimental genetics
6. Physiological genetics	15. Genomics
7. Pharmacogenetics	16. Transcriptomics
8. Oncogenetics	17. Proteomics
9. Immunogenetics	
Clinical Genetics	
1. Chromosomal aberrations	12. Genetic diseases of the muscular system
2. Congenital malformations	13. Genetic diseases of the skeletal system
3. Inborn errors of metabolism	14. Genetic diseases of the blood
4. Mitochondrial disorders	15. Genetic diseases of the immune system
5. Genetic systemic syndromes	16. Genetic diseases of male reproductive system
6. Genetic diseases of the nervous system	17. Genetic diseases of female reproductive system
7. Genetic diseases of the endocrinal system	18. Genetic diseases of the eye and vision
8. Genetic diseases of the cardiovascular system	19. Genetic diseases of the ear and hearing
9. Genetic diseases of the respiratory system	20. Genetic diseases of the skin
10. Genetic diseases of the GIT system	21. Genetic psychiatric disorders
11. Genetic diseases of the urinary system	
Diagnostic Genetics	**Prophylactic Genetics**
1. Molecular diagnostic techniques	1. Premarital prophylaxis
2. Cytogenetic diagnostic techniques	2. Preconception prophylaxis
3. Biochemical diagnostic techniques	3. Prenatal prophylaxis
	4. Presymptomatic prophylaxis
Therapeutic Genetics	**Applied Genetics**
1. Pharmacological therapy	1. Genetic counseling
2. Nutritional therapy	2. Genetic screening
3. Enzyme replacement therapy	3. Preimplantation diagnosis
4. Organ transplantation therapy	4. Prenatal diagnosis
5. Surgical intervention	5. Fetal Therapy
6. Stem cell therapy	6. Forensic genetics
7. Genetic therapies	7. Genetic engineering
8. Conventional therapies	8. Eugenics

Table 1: Spectrum of medical genetics.

The nuclear genome in each human germ cell; ovum and sperm, is organized into a set of 23 separate chromosomes known as the haploid genome which represents the unit genome of humans. The haploid genome of the ovum consists of 22 chromosomes that do not participate in sex determination and referred to as the autosomes, and one sex determining X chromosome. Similarly, the haploid genome of the sperm consists of 22 autosomes, and one sex determining X or Y chromosome. Upon fertilization, both haploid genomes of the sperm and the ovum constitute a diploid genome consisting of their 46 chromosomes, 44 autosomes and 2 sex determining chromosomes, either XX in females or XY in males. The diploid genome characterizes the nuclear genome of the zygote as well as all somatic cells descendant from it. With very rare exceptions, mitochondria of the sperm do not participate in fertilization, being carried in the neck piece of the sperm which do not penetrate the ovum. Nearly, all mitochondria, and hence the mitochondrial genome, present in the zygote and in all body cells are descendent from the mitochondria present in the ovum. This feature accounts for the phenomenon of maternal inheritance, a non-traditional mode of inheritance of genetic diseases caused by mutations of the maternal mitochondrial genome. Maternal inheritance of genetic diseases or traits occurs also for nuclear genes carried on the X chromosomes of the mother due to the process of Lyonization, or suppression of all X chromosomes in the cell in excess of one and underlies the characteristic inheritance patterns of X linked recessive and dominant genetic disorders.

Nuclear genes are arranged in a linear sequence on chromosomes. The estimated 20000-25000 genes that comprise the nuclear genome constitute, and are distributed over, the 46 chromosomes in the nucleus. The larger and longer chromosomes have far more numbers of genes than the smaller and shorter chromosomes. Because genes constitute only a small proportion of the whole genome, they are separated by long inter-genic regions of base sequences of the DNA that comprise most of the non-genic or gene-related components of the genome. These include: pseudo-genes, pyknons, transposons and telomeres in addition to an exceedingly large numbers of long and short repetitive and non-repetitive interspersed elements, among many other components of, yet, undefined function(s) [3].

The human mitochondrial genome exists in varying numbers, tens to thousands, of very small closed circular double stranded structures inside the mitochondria. The number of mitochondria and the number of mtDNA molecules in each mitochondrion varies according to the metabolic activities of the cell. The most active and energy-demanding cells, like neurons, heart muscles, the retina, skeletal muscles, endocrine glands, kidney cells and liver cells have the largest numbers of mitochondria within their cytoplasm and the largest numbers of mtDNA molecules in each mitochondrion as well. Each molecule of the mitochondrial genome consists exclusively of 37 genes. Though it constitutes very tiny fraction of the whole genome, mtDNA is indispensable for life because it codes, with other nuclear genes, for proteins that mediate ATP production in the cell via a specific oxidative phosphorylation network. In addition, mtDNA regulates synthesis of proteins that mediates many important metabolic activities of living cells like lipid oxidation and steroid biosynthesis. More importantly, it participates with nuclear genomic components in controlling apoptosis. Due to increased susceptibility of mitochondria to mutational events and limited mitochondrial genome repair capabilities, accumulating mutations of mtDNA are linked to functional deterioration and enhanced aging of cells.

Genes of the human nuclear genome can be classified into three main categories: structural genes which are directly involved in synthesis of proteins, regulatory genes which regulate the function of structural genes through transcription enhancing/silencing factors and master genes which are responsible for maintaining the stability and integrity of the genome through regulating major vital functions of the cell like cell division, DNA repair and apoptosis. Structural genes constitute the largest portion of the genome and function in a stepwise manner composed of six consecutive stages: gene activation, transcription, post-transcription modifications, translation, post-translation modifications and intracellular trafficking and targeting of synthesized protein. Though traditional concepts of gene function do not include the last two stages concerned with structural modifications and intracellular localization of translated proteins, although both of these processes are, and should be considered as, integral stages of gene

function because many genetic disorders result from defects in either of these steps in spite of synthesis of the protein product of the gene in normal amount with normal primary structural configuration.

Types of Genetic Diseases

Genetic disorders comprise many different types and are classified into many different categories according to their causes and their clinical manifestations. The great majority of currently defined disorders result from defects in nuclear genes carried on chromosomes. Some of these disorders might result from defect in one gene only; single gene disorders, others might develop due to combined defects in many genes; polygenic disorders. Defects in mitochondrial genes result in pathogenesis of distinct group of diseases referred to as mitochondrial disorders. Since ATP production in cells depends on a metabolic network mediated by proteins and enzymes produced by both nuclear and mitochondrial genes, a peculiar group of diseases characterized by deficient energy production and known as oxidative-phosphorylation disorders results from deficient production or production of defective proteins mediating ATP production.

Chromosomal disorders are, in essence, polygenic disorders due to involvement of very large numbers of genes according to the magnitude of the underlying pathogenetic mechanism(s). They are classified into autosomal anomalies due to defects in the autosomes and sex chromosomal anomalies. Each of these types might present as structural disorders caused by structural chromosomal abnormalities or as numerical disorders due to presence of abnormal number of chromosomes in the nucleus. Structural chromosomal abnormalities comprise many pathological types like translocations, deletions, inversions, duplications, ring chromosomes, isochromosomes and chromosomal fragility. Numerical chromosomal abnormalities, which result due to defects in chromosome number, also include many types according to whether they result from autosomal or sex chromosome abnormalities. Pathological examples of this category include trisomy, or existence of an extra copy of the chromosome, monosomy, or deficiency of a chromosome which is limited only to the X chromosome in Turner syndrome, hypodiploidy, where less than the normal diploid number of chromosomes (46) exists in the nucleus and hyperdiploidy where larger numbers of chromosomes exist in the nucleus. Extreme hypodiploidy and hyperdiploidy are cytogenetic anomalies characteristic of malignant cells.

Genomic disorders represent another group of genetic diseases due to defects involving the whole genome, instead of one or few genes. They can be classified, in turn, into numerical genomic disorders and functional genomic disorders. Numerical genomic disorders are exemplified by polyploidy and comprise triploidy where three sets of the haploid genome (69 chromosomes) exist in the nucleus and, less frequently, tetraploidy characterized by presence of four sets of the haploid genome (92 chromosomes) in the nucleus. These aberrations are, mostly, caused by defective genomic regulatory mechanisms, e.g. endoreduplication, where DNA replication is not synchronized properly with corresponding stage of cell division. Functional genomic disorders are caused by defects in regulatory mechanisms, e.g. genomic imprinting, responsible for controlling, regulating and synchronizing genome function in the very early stages of development and can present as vesicular moles and dermoid cysts. A portion of early miscarriages might be due to functional genomic defects interfering with survival of the affected embryo.

Multifactorial disorders constitute a specific category of genetically-determined disorders and anomalies caused by the combined effects of environmental teratogens on defective or susceptible genetic background. These disorders encompass some of the most common and prevalent diseases among most populations like hypertension, diabetes mellitus, and many types of cancer, many psychiatric disorders and a very large variety of congenital malformations of nearly all body organs like cleft lip/cleft palate, pyloric stenosis and multiple congenital heart defects.

Genetic systemic syndromes include diseases characterized by affection of multiple organs, sometimes even many systems of the body. Many single gene disorders and most chromosomal aberrations present with widespread involvement of many organs and systems, systemic genetic syndromes are not caused by either of these mechanisms. Some of these disorders, however, might be caused by still undefined single genes or by some other unknown mechanisms causing multiple simultaneous functional deficiencies of many components of the genome. Defective regulatory mechanisms exerted by microRNA subclasses over many genes at the same time might be another possible underlying factor that can be implicated in pathogenesis of these systemic syndromes.

Medical Pathogenetics

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

Pathogenesis of genetic diseases

Genetic diseases are caused by mutations. Mutations are defined as uncoded or unprogrammed permanent structural alteration of the genetic material affecting any of its organizational levels. These levels comprise a wide range beginning with a whole nucleotide or just part of it (base, sugar, phosphate), DNA, RNA, genes, chromosomes, mitochondrial DNA (mtDNA), up to the whole genome. This cause and effect relationship between mutagens, mutations and genetic disorders spans a very wide spectrum of different mechanisms that follow a peculiar cascade of events beginning with mutation-induced pathogenetic alterations of the genetic material, leading to disturbed gene function and deficient or improper synthesis of gene products, whether these products are proteins or small regulatory miRNA biomolecules. The ensuing defects in functioning of the regulatory and metabolic networks that control cellular activities result in development of multiple and variable defect-specific pathophysiological derangements that culminate in pathogenesis of genetic disease.

Mutagens

Mutagens are factors that can cause mutations. Mutagens are plentiful in our life. In fact, we live and survive in a mutagenic world, and probably with the exception of pure water, any compound in our environment could be a potential mutagenic factor under favorable circumstances. Mutagens can be classified according to their nature or according to their recognizable pathogenetic and pathophysiological effects on exposed cells. According to their nature, mutagens are classified into four main categories: chemical mutagens, physical mutagens, biological mutagens and changes of structural configuration of bases of DNA and changes in energy states of bonds between these

bases [4]. Classification of mutagens based on their effects recognizes four major groups: non-specific mutagens, carcinogens, clastogens and teratogens (Table 2).

Types of mutation

Mutation might be classified to many different types according to the parameters used for classification which include the nature, the target, the magnitude and the effect of the mutational event, among many other criteria (Table 3). The effects of mutation differ widely according to many factors. These factors include the nature and target of the mutagenic factor causing the mutation, the timing and magnitude of the resulting damage, the genetic constitution of the affected individual and the balance between synergistic mutagenic effects and anti-mutation mechanisms of the genetic material. The damaging effects of mutation are attributed to the defects they cause in functioning of mutated genes. Since synthesis of proper gene products, necessary for mediating cellular activities, depends primarily on integrity of the genetic information embodied within the specific base sequence of the gene, changes or mutation of the exact number or the peculiar arrangement of these bases is expected to result in deficient or disturbed gene function. This disturbance might express itself as production of structurally defective gene product, deficient synthesis of enough product or disturbance in regulatory mechanisms responsible for mediating, monitoring, harmonizing and controlling gene functions.

Somatic mutations refer to mutations of the genome of somatic cells. The effects of somatic mutations depend on many factors including the type of cell, the genetic constitution of affected cells, selective targeting of nuclear and/or mitochondrial genome and the mutation burden of the cell. According to the interactive processes involving these factors, somatic mutations might result in cell death if the mutation-induced pathophysiological alterations of the cell exceed its ability to obviate and correct these alterations. Milder alterations can cause deranged cellular function(s) and limited or progressive failure and loss of cellular activities, e.g. progressive organ failure syndrome

According to effect	According to nature	Examples	Mechanisms and effects
1. Carcinogens Mutagens that induce malignant transformation and development of cancer 2. Clastogens Mutagens that cause breakage of chromosomes 3. Teratogens Mutagens that cause congenital malformations in developing embryos 4. Non-specific mutagens Mutagens that cause non-specific mutagenic damage to the genetic material.	1. Physical mutagens	1.Particulate radiations: X- ray, alpha particles, neutrons, positrons, gamma rays, protons. 2. UV waves 3. Solar radiation & electromagnetic waves 4. Thermal exposure 5. Mechanical agitation	1. Breakage of nucleicacids 2. Chromosome breaks 3. Oxidation of deoxyribose 4. Formation of peroxides 5. Deamination of bases 6. Dehydroxylation of bases 7. Ionization and formation of ion tracks/ion clusters 8. Generation of freeradicals 9. Provocation of carcinogenesis 10. Formation of pyrimidine dimers 11. Denaturation of DNA
	2. Chemical mutagens	Organichydrocarbons, acridine derivatives, manganese, nitrous acid, hydroxylamine, base analogs, sulfonate compounds, insecticides, asbestos, herbicides, heavy metals.	1. Base transition 2. Base transversion 3. Deamination of bases 4. Generation of free radicals 5. Interruption of base Sequence by intercalation 6. Provocation of carcinogenesis 7. Cytopathic effects following mitDNA damage 8. Alkylation 9. Adduct formation
	3. Biological mutagens	1. Viruses: rubella virus, cytomegalovirus, HIV and herpes virus. 2. Toxoplasma gondii.	1. Insertional mutagenesis 2. Provocation of carcinogenesis
	4. Change of bases/energy States of bases of DNA	Tautomerism, Hydration of bases	Base transition
	5. Metabolic derangements	1. High acidity 2. Dehydration 3. Peroxidation	Depurination of nucleic acids Provocation of aberrant DNA replication.

Table 2: Classification of mutagens.

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. Persistent versus reversible mutation
7. Point, Small, Gross, Genomic mutation
8. Base, Sugar, Phosphate group mutation

Table 3: Classification of different types of mutation.

following overexposure to radiation. Somatic mutations affecting the proto-oncogenes or genes regulating DNA repair systems can result in malignant transformation of the cell and development of cancer.

Germinal mutations, on the other hand, are mutations that affect genomes of germinal cells that participate in fertilization and determination of the genetic constitution of the offspring. If the particular ovum or sperm affected by the mutation happens to participate in fertilization and zygote formation, the mutation will be inherited and transferred to all cells of the offspring, and a carrier or disease state might result according to the nature of the mutated gene and the pattern of its inheritance.

Static mutations are mutations that are transferred to offspring of carriers of these mutations without change. For instance, if a child inherits the mutated gene causing, e.g. Marfan syndrome, from an affected parent he will have the same mutation of the inherited gene in his genome. Dynamic mutations, on the other hand, signify mutational events that increase in magnitude upon transfer from carriers of these mutations to their offspring. This type of mutation characterizes a large, ever expanding number of widely varied peculiar groups of genetic disorders collectively referred to as triplet repeat expansion disorders. In this specific type of mutation, microsatellite repeats consisting of certain number of codons, or triplets, of a parental gene increases in number upon transfer to an offspring. If the increase, or expansion, attains a certain threshold, the offspring becomes a carrier of the dynamic mutation. Further transfer to offspring of next generations results in much wider expansion, or pathological increase of the number of the repeats in the gene leading to damage of gene structure and interference with gene function, thus leading to development of genetic disease due to this pathogenetic mechanism of triplet repeat expansion.

Fragile X mental retardation syndrome represents the prototype of this category of genetic disorders due to triplet repeat expansion. Normally, the FMR gene, existing on the terminal region of the long arm of the X chromosome, regulates the synthesis of an important protein necessary for functioning of many organs, including the brain. In normal subjects, the gene has nearly 5-50 CGG repeats. Female carriers of this gene in its mutated form have between 120 up to 200 repeats, a state known as premutation state. Affected male offspring of these carrier females have much larger numbers of these repeats, more than 200 up to few hundreds, in their gene. This triplet repeat expansion results in disruption of gene structure and interference with gene function through different pathogenetic mechanisms, e.g. chromosome instability or fragility, all ending in either suppression of transcription and deficient synthesis of the gene product or synthesis of defective product, thus leading to development of disease. Triplet repeat expansion disorders comprise large number of diseases differing from each other according to the mutated gene. Each of these diseases has its specific repeat sequence and threshold number for its development. For example, the triplet of Huntington disease and some types of spinocerebellar ataxia is CAG while that of Friedreich ataxia is GAA. In view of the specific nature of mutations of these diseases, they are inherited in nontraditional way and account, at least in part, for the phenomenon of genetic anticipation.

Pathological versus non-pathological mutations: The deleterious effects of mutation are determined by many factors. Mutations affecting functional elements of the genome, i.e. functional genes, can result in gene dysfunction causing deficient synthesis of the gene product or synthesis of defective product. These mutations are expected to cause pathophysiological changes and disease phenotypes in affected individuals, and represent an overt example of harmful pathological disease-causing mutations. On the other hand, mutations affecting non-functional regions of the genome, e.g. intergenic areas of DNA and intronic segments of genes, do not result in pathophysiological alterations and are referred to as non-pathological mutations.

The concept of protein domain and its relation to effects of mutation

The amino acids that constitute each protein are organized, both structurally and functionally, into distinctive number of interrelated, sometimes interactive, regions or domains. Each domain consists of a defined number of certain amino acids arranged in a specific manner, and performs a particular role either in shaping and maintaining the structural configuration of the protein (structural domain), or in mediating one or more of the biological function(s) of the protein (functional domain). Each protein has its own specific structural configuration as regards the number, the spatial arrangement and distribution of its domains. In view of their fundamental role in maintaining structural and functional integrity and identity of the protein, protein domains are highly conserved among most species [5].

Mutation results in change(s) of one or more of the protein domains depending on the type of the mutation, the magnitude of its effects and the nature of the protein encoded by the mutated gene. If mutation affects one or more or all of the amino acids constituting integral structural and/or essential functional domain of the protein, deleterious defects in protein function results. This pathogenetic mechanism paves the way to significant detrimental effects on the functional integrity of the protein. If the affected protein mediates specific roles in cellular activities, e.g. structural components of cell organelles or signal transducer in metabolic networks, pathophysiological alterations secondary to loss of these roles ensue with consequent pathogenesis of genetic disorder. Alternatively, depending on the nature, the effects, the site and the magnitude of the causative pathogenetic mechanism, some mutations might primarily affect non-critical or non-integral domains of the protein. These mutations usually result in subtle conformational changes, e.g. changes in the molecular weight or the electrophoretic mobility of the protein that do not impede, or interfere with, the physiological functions of the protein, and do not cause disease since they do not significantly disturb the form-function relationship that confers on each protein its biological potency. Thus, the effects of genetic mutations are largely dependent on the resulting effects on the structural integrity as well as the functional capability of the protein. This fact clarifies, at least in part, the marked variability in potential of genetic mutations in causing disease and explains absence of any disease manifestations in spite of presence of mutation in many situations.

Pathogenetic Mechanisms

The genetic material controls life activities of the cell through regulating 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. 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 development of genetic disorders, secondary to the ensuing pathophysiological alterations of cellular functions.

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 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 our knowledge of our genetic material.

Currently defined pathogenetic mechanisms and pathophysiological alterations implicated in pathogenesis of genetic disorders are too many to be listed. However, the most common of these mechanisms 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/rearrangement of chromosomes

6. Deficient transcription of mRNA

7. Transcription of defective mRNA

8. Deficient/defective post-transcription mRNA repair

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

22. Defective imprinting

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 disposal of metabolic waste products (storage disorders)

    e. Deficient/defective regulation of intra and inter network reactions and interactions: signal transduction disorders

    f. Deficient/defective positioning of structural proteins (protein trafficking disorders)

    g. Deficient/defective production of cellular energy: oxidative-phosphorylation disorders

    h. Ubiquitination/proteasome degradation defects

    i. Apoptosis defects

Anti-mutation Mechanisms of the Human Genome

The human genome develops, persists and works in a hostile environment full of existing, and continuously generated, mutagens. Mutational events induced by external mutagens 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 quite impossible.

The human genome is endowed with a spectacular multifaceted strong anti-mutation system responsible for maintaining its stability and integrity, as well as 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 and developing 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 (Table 4).

Structural organization of the human genome

The peculiar structural organization of the human genome represents the first innate anti-mutation mechanism in view of the presence of large interspersed portions of non-functional intragenic introns and inter-genic DNA sequences and segments that can be mutated without having appreciable deleterious functional effects. In addition to functional sequences needed for synthesis of protein and of regulatory small RNA species, the human genome has a considerable amount of repetitive DNA sequences, including both noncoding

Mechanism	Types and pathways and 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.

Table 4: Anti-mutation mechanisms of the human genome.

repetitive sequences and multiple copy genes and gene fragments, a large number (19000-21000) of pseudogenes [6], a considerable sizable portion (about 1/6th of the total genome size) as pyknons [7], a quite large portion (nearly 40% of the total genome size) as transposons [8], and large numbers of multiple copies of functional genes that share the same regulatory function and whose suppression or damage by mutation can be tolerated by other genes having the same function. These peculiar structural features of the human genome allows for occurrence of mutational events in many segments of the genome without having appreciable functional defects. Even if some of these DNA sequences have important roles in genome function, their presence in multiple repetitive copies can greatly reduce, or even nullify, the consequences of mutational damage.

The mitochondrial genome

The presence of multiple copies, hundreds to thousands, of mitochondrial genes within the mitochondria of each cell is crucial in obviating devastating mutation-induced damage to these vital organelles in view of their role in production of ATP. This feature of mitochondrial genome allows for considerable burden of mutations to affect it before appreciable pathological consequences result. It is estimated that mutations affecting nearly 80% of certain mitochondrial genes might occur before pathological manifestations of mitochondrial genetic diseases make their appearance due to this multiple copy feature of mtDNA.

Structural features of DNA

DNA exists as a double stranded structure composed of two tightly bound strands, each strand consisting of a sugar-phosphate backbone with opposing nitrogenous bases each linked by a glycosidic linkage to the sugar of its parent strand and by hydrogen bonds to the complementary base on the opposing strand. This specific structural organization of DNA serves many purposes. It stabilizes the dynamics of the molecule, permits replication and duplication of the genetic material, protects the interiorly located bases and, most importantly, stores a template or copy of the genetic information ready for use in case of damage of the other strand. If small or gross mutational events affect important functional portions of the genetic material, repair mechanisms can restore the exact sequence of the damaged or lost or deleted parts through restoration mechanisms based on the complementary information of the other strand. Mutations leading to damage of corresponding segments of both strands represent a catastrophic event to the genome due to absence of the sequence database needed for the repair mechanism to define the exact base sequence of the newly synthesized segment in place of the deleted or grossly damaged segment.

Degeneracy of the genetic code

Degeneracy of the genetic code represents the third innate anti-mutation mechanism of the human genome. This feature permits the occurrence of same-sense point mutations in functional codons without changing the amino acid defined by the mutated codon. Since some amino acids, as part of a specific protein domain, play critical roles in attaining and maintaining correct protein structure and mediating proper protein function, mis-sense point mutations leading to replacement of these essential amino acids by other amino acids that can't perform the functions of the original amino acids might result in detrimental effects on the structural integrity and stability of the protein followed by deleterious consequences on its physiological function. Hence, degeneracy of the genetic code allows for occurrence of many point mutations, the commonest type of mutational events and the commonest cause of genetic disorders, without changing the final structure of the synthesized protein, thus protecting against, and obviating, the pathological effects of these mutations.

Nuclear localization of DNA

The localization of DNA, deeply inside the cell nucleus, represents a fourth innate anti-mutation mechanism of the human genome because it acts as a physical barrier against many mutagens that have to overcome many obstacles of cellular defense mechanisms in order to affect the nuclear genome. These defenses include the extra-cellular environment, the cell membrane, the cytoplasmic, the cytoplasmic enzymes and phagocytic cellular organelles and the cytoplasmic and nuclear antioxidant enzyme systems. The DNA-associated or DNA-binding proteins, in addition to their essential roles in regulating transcriptional processes of most genes, also play fundamental roles in protecting the DNA from the damaging effects of many mutagens, in particular the free radicals that are generated during metabolic activities of the cell. They act as firm physical barriers and strong biochemical buffers that effectively modify and deactivate biomolecules of many chemical mutagens or damaging factors that might harm the DNA. They mediate this protective role through many mechanisms including modulation of charge transport of oxidative agents within the DNA, limitation of DNA helix distortion and regulation of protein-dependent alterations in DNA base stacking [9].

RNA-proofreading System

The human transcriptome, being subjected to the same mutational events that can 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. Separate RNA-proofreading system seems to exist and act, probably, during transcription by relying on the sequence complementarity information of the complementary silent or non-transcribing strand of DNA, rather than of the active transcribing strand. This behavior can be interpreted, partly, by classic principles of thermodynamics because relying on the sequence of the energetically active, transiently unstable, strand to ensure accurate transcription might result in improper defective transcription if mismatch errors occur due to, e.g. polymerase dysfunction. The risk of faulty transcription depending on the sequence complementarity information of the less energetic, more stable, non-transcribing strand is, probably, less than comparable risk expected to occur if transcription depends on the sequence complementarity information of the active strand. This assumption might, partly, offer reasonable explanation for the poorly understandable behavior of gene function where transcription of complementary mRNA, instead of straightforward synthesis of identical mRNA transcript, is the rule. It might also explain the seemingly needless, indirect and energy consuming processes involving transcription of complementary, rather than identical, mRNA transcripts that have to be decoded again by rRNA and tRNA in the ribosome during translation. Expenditure of energy for keeping transcriptome integrity is consistent with general rules of thermodynamics since maintaining stability of any structured system is dependent on the equilibrium between its natural tendency to degrade and external energy supply needed to keep it in a stable form.

Replication proofreading system

Preservation of genomic identity of the organism depends exclusively on accurate replication and synthesis of two identical copies of the genome during cell division, followed by transfer, or inheritance, of each copy to each daughter cell. In this manner, all cells descendent from a parent cell have nuclear genomes identical to that of the parent cell. The majority of spontaneous point mutations of the nuclear genome are prone to occur during cell division, mostly during DNA synthesis or the replication phase of the process. The replication proofreading system acts in a prophylactic way to ensure accurate insertion or addition of the proper nucleotide to the newly synthesized strand of replicating DNA. This prophylactic function is fundamental to reduce the rate of inevitable replication mistakes to minimum levels that could be dealt with efficiently with the DNA repair mechanisms. In spite of the impressively fast and accurate ability of the enzymes responsible for DNA synthesis, DNA polymerases, most of them have additional proofreading ability to ensure accurate error-free DNA replication and, hence, maintaining and preserving the stability, integrity and identity of the genome during cell division, as well as during transfer of the genetic material from parents to offspring.

Genetic repair systems

Genetic repair systems responsible for correcting and repairing many different types of point and small mutations comprise both nuclear DNA repair system and mitochondrial DNA repair system. Genetic function and genetic repair represent two sides of the same coin. Without the persevering continuous, active and effective surveillance exerted by the genetic repair systems to detect and repair the continuously and persistently occurring mutations, maintaining stability and integrity of the genome would be an impossible task. These repair systems act via many different mechanisms according to the type, location and magnitude of damage induced in the genetic material [10].

The pivotal role played by the mitochondrial genome in generating ATP, without which life can neither begin nor persist, in addition to the many other critical metabolic and regulatory functions of mitochondrial genes, requires the presence of an efficient system for repairing mtDNA mutations. The need for mitochondrial genome repair system is further imposed on the cell in view of the high mutation rate of mitochondrial genes which lack many of the anti-mutation and protective mechanisms available to nuclear genes. Similar to the nuclear genome repair system, mitochondrial repair system includes many repair pathways and mechanisms: base excision repair, direct reversal repair, mismatch repair, and recombination repair. Nucleotide excision repair (NER) pathway, however, seems not to be working in the mitochondria [11].

RNA repair/editing system

RNA editing refers to molecular modifications of nucleotides of RNA through chemical changes in the base makeup of the molecule. Such changes appear to involve mRNA, tRNA as well as many types of small or microRNA. RNA editing occurs in the cell nucleus and the cytosol, as well as in mitochondria and is mediated by a complex repair system comprising many species of small RNA (guide RNA) and large protein complexes known as the editosomes. The pathways and mechanisms of RNA editing include many diverse processes: nucleoside base modifications such as cytidine (C) to uridine (U) and adenosine (A) to inosine (I) deamination, as well as non-templated insertions of nucleotide. RNA editing in mRNAs effectively alters the amino acid sequence of the encoded protein so that it differs from that predicted by the genomic DNA sequence. Though mRNA editing is used by the cell in many instances to allow for synthesis of more than one protein from the same mRNA transcript, e.g. synthesis of both apolipoprotein B-100 and apolipoprotein B-48 from the same mRNA in liver cells, it can also be used to repair missense or termination mutations of the molecule which can have deleterious effects on the synthesized protein. Specific endonucleases and ligases for double stranded species of RNA have been defined in many prokaryotes [12] and it might be just a matter of time before defining their functional counterparts in eukaryotes and human cells.

Protein repair systems

Accurate post-translation structural configuration of newly synthesized polypeptide chains is a fundamental conformational modification for most proteins to become functionally active biomolecules. The maturation from primary to quaternary protein structure involves many changes, e.g. folding and maintenance of steric and spatial relationships between the different domains of the protein. Conformational defects in proteins that might happen during these modifications can lead to formation of misfolded and/or aggregated non-functional molecules. The human genome comprises a large number of genes that code a complex system composed of large numbers of specific protein families and subfamilies known as molecular chaperones. These proteins have many important and diverse functions in cellular activities, e.g. assisting non-covalent folding or unfolding and assembly or disassembly of macromolecular structures, including proteins. Prevention of misfolding and/or aggregation of newly synthesized polypeptide chains, which turn them to nonfunctional biomolecules, is a major and fundamental function of molecular chaperones. Other physiological functions of chaperones include: transport across mitochondrial membranes and

the endoplasmic reticulum and assistance in protein degradation [13].

Molecular chaperones, probably, exert critical roles in maintaining stability and integrity of the proteome. This state of protein homeostasis, proteostasis, is a prerequisite for proper control and regulation of cellular metabolic networks by proteins and is mandatory for efficient mediation of cellular activities. Specific species of molecular chaperones, surveillance chaperones, are responsible for constant surveillance of the proteome to ensure proper protein homeostasis. Age-related decline or mutation-induced defects in proteome stability and integrity results in progressive aggregation and faulty conformational changes of proteins, both of which are associated with, and underlie, the development and pathogenesis of many genetic diseases like Alzheimer disease, Parkinson disease, prion diseases and many others [14].

Silencing of transposon activity during development

Transposons constitute a considerable portion, nearly 40%, of the human nuclear genome. Transposon activities might have contradictory effects on the stability and integrity of the nuclear genome. They might behave in a harmful way and act as major potential causes of spontaneous mutations of the nuclear genome. They can make a copy of themselves and insert the new copy in another site, or they can detach themselves from their location and get inserted at different sites of the genome. In both conditions they result in insertional mutagenesis with consequent deleterious effects on genomic stability and genomic integrity. If they get inserted in a functional segment of the genome they lead to structural disruption and loss of function of the affected segment with resultant pathological effects. Hence, over activity or uncontrolled activity of transposons can have detrimental and devastating effects on embryogenesis, differentiation and development, and can lead to pathogenesis of a wide variety of congenital malformations and genetic defects [8]. The human genome, however, has a unique control system composed of a specific subtype of small or micro RNA molecules, known as piwiRNA, or piRNA, composed of RNA-piwi protein complexes. They are thought to be involved in gene silencing, most specifically the silencing of transposons. The majority of piRNAs are antisense to transposon sequences suggesting that transposons are the main target of piRNA. In mammals, the marked activity of piRNAs in silencing of transposons and control of their activities is most important during the development of the embryo in order to reduce the rate and risk of transposon-induced mutations during this sensitive period of life [15].

Alternatively, transposon activity may lead to creation and construction of new genetic combinations that may have specific functions. Within this context, they would be considered as one of the genetic biological mechanisms involved in, and responsible for, evolutionary diversity of the genome and the proteome. They can also cause tangible increases in the amount of the genetic material due to recurrent synthesis and addition of multiple new copies of transposable elements to the nuclear genome.

Antioxidant enzyme systems

The continuous functioning of the exceedingly huge number of metabolic networks that mediate cellular activities in living cells results in continuous generation of many different types of useful as well as of harmful metabolic by-products. Oxidant free radicals constitute one of the most crucial categories of these harmful by-products in view of their ability to induce widespread damage in many cellular components including membranes, organelles and structural macromolecules like lipids and proteins. This structural damage, unless counteracted by

opposing antioxidant mechanisms, results in progressive degradation of cellular constituents with consequent resultant pathophysiological alterations of cellular functions, leading ultimately to disease. Although low concentrations of reactive oxygen species may be beneficial, or even necessary in mediating many important cellular processes, e.g. defense against invading micro-organisms and intracellular signaling pathways, nevertheless, higher concentrations of these free radicals play a causative role in the aging process as well as in pathogenesis of many human diseases, including immune deficiency, neurodegeneration and malignancy. Oxidative damage of DNA, RNA and binding proteins by free radicals represents an important category of detrimental genetic mutations induced by endogenous chemical mutagens inevitably generated during cellular metabolic activities and other cellular functions. Living cells have several efficient non-enzymatic and enzymatic antioxidant activities that are responsible for eliminating and/or terminating the chain reactions following generation of free radicals, as a safeguard against their damaging effects on cellular components and cellular functions. Enzymatic antioxidant systems of the cell comprise many different types of antioxidant enzymes, notably superoxide dismutase, catalase, thioredoxinreductase, glutathione peroxidase and various other peroxidases. Efficient production of these antioxidant enzymes and proper regulation of their functions is mandatory to protect both the genome and proteome and to keep and maintain redox homeostasis of the cytoplasm which is a critical requirement for normal mediation of cellular activities [16].

Apoptosis

Apoptosis refers to programmed cell death and represents a universal biological behavior of most living cells necessary, in conjunction with other life-regulating mechanisms, for maintaining the vital balance between life and death that governs optimal life conditions of multicellular organisms. Apoptosis plays fundamental and crucial roles in normal growth and development as well as in normal differentiation and determination of the proper final structural architecture of cells, tissues and organs. Faulty timing or incorrect accomplishment of specific and selective apoptotic processes during specific life stages of the cell might result in devastating consequences on cellular functions that range from dysfunction to malformation. For instance, improper regulation of apoptosis during embryonic and fetal life can lead to the development of many types of congenital malformations. In many conditions, it might ultimately culminate in pathogenesis of disease or in premature cell death [17].

Apoptosis plays a crucial role in maintaining genomic stability and integrity, not of individual cells, but of the organism as a whole. Induction of apoptotic mechanisms in heavily mutated or lethally mutated cells leads to death of the cell and prevents transfer of these mutations to its putative descendant daughter cells. This fundamental prophylactic anti-mutation role of apoptosis in cellular activities and life prospects of living organisms has more far-reaching effects on many important aspects related to the balance between, and the incidence of, normal and mutant genotypes within species-specific gene pools. Additionally, apoptosis can affect in an appreciable manner genomic identity of living organisms because mutation-induced evolutionary or decadence pathways are largely dependent on the outcome of certain apoptotic mechanisms operating during certain stages of the cell cycle.

Apoptosis may be looked at as a special genomic protective pathway involving compulsory death of somatic cells overburdened with mutation. Over mutated cells are driven to their ends through specific apoptosis-mediating pathways to protect other cells from the hazardous risks of their malignant transformation. Apoptosis might,

also, represent a cellular economic adaptation behavior by getting rid of mutated, diseased, energy consuming and non-functioning harmful cells. In this way, it performs important protective anti-mutation mechanism to maintain genomic integrity through executing and getting rid of heavily mutated cells, to prevent spread of their mutations, through division, to daughter generations.

Melatonin

Melatonin is a hormone synthesized by the pineal gland, bone marrow cells, epithelial cells and lymphocytes. Melatonin receptors are distributed in most organs, a finding reflecting its widespread roles in regulating various physiological and psychological processes. Many *in vitro* and animal studies revealed that melatonin has diverse functions including effective protection of cells against radiation-induced chromosome breakage and inhibition of tumor development in animals exposed to experimental chemical carcinogenesis. Melatonin was shown to have protective effect against oxidative DNA damage by chemical inactivation of DNA-damaging agent as well as by stimulating DNA repair mechanisms. These important anti-mutagenic and anti-clastogenic effects of melatonin can be linked with its ability to protect DNA against oxidative damage. It may exert this antioxidant action by eliminating harmful reactive oxygen radicals or by stimulating the repair processes of oxidative stress-induced damage of DNA [18].

Patterns of Inheritance

The specific patterns of inheritance of genetic diseases describe the characteristic features which outline, control and regulate the transmission of genetic diseases from normal, carrier or affected parents to their offspring. These features vary widely according to the actions and interactions of many factors in addition to many other modifying conditions.

Genetic diseases are inherited in many different way depending on many variable factors that include the cause of the genetic defect whether due to single gene disorder, polygenic disorder, mitochondrial mutation, chromosomal aberration or multifactorial causation, the gene locus whether it lies on an autosome or on a sex chromosome, the nature of the gene product whether it is a structural protein or a catalytic enzyme, the nature of the underlying mutational event whether it is a static or a dynamic mutation, the status of the transmitting parent(s), the causative pathogenetic mechanism(s) underlying the development of the disease and whether this transmission happens in a classic traditional manner or within the context of an abnormal genetic framework [19-22]. However, two major patterns of inheritance of genetic diseases could be recognized: classic, Mendelian or traditional patterns that characterize rules of inheritance of single gene disorders, and non-classic, non-mendelian or non-traditional patterns that delineate features of inheritance of other types of genetic diseases (Table 5) [23].

The locus of the mutant gene defines four different categories of single gene disorders each having its own specific pattern of inheritance: autosomal diseases caused by genes located on the autosomes, X-linked diseases caused by genes located on the X chromosome, Y-linked diseases caused by genes located on the Y chromosome and mitochondrial disorders caused by mutations of mitochondrial genes.

The status of the transmitting parent, or both parents, determines many different aspects of the pattern(s) of inheritance of the disease. For single gene disorders, five main patterns of inheritance based on the way of transmission of the single mutant gene relative to the status of the transmitting parent(s) are recognized. These patterns include: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive and Y-linked inheritance patterns.

For human traits and diseases, dominance refers to the ability of the mutant gene to confer a specific phenotype on the individual harboring it when present in a single copy or allele. Recessive genes need to exist in two copies, or alleles, in order that a specific recessive disease or trait phenotype can show up. The difference between dominant and recessive diseases can be attributed, in part, to the different underlying pathogenetic mechanisms and might be explained in view of the specific pathological characteristics of each type since dominant diseases result, mostly, from deficient and/or defective production of structural proteins produced by mutant genes. These structural proteins are vital integral constituents of nearly all cellular components, e.g. cell membranes, cytoskeleton, cell organelles, spindle apparatus, chromatin material and mitochondrial components. In autosomal dominant (AD) diseases, nearly 50% reduction in amount or functions of structural proteins happens which represents a drastic burden that can't be tolerated by the cell, hence the expression of the disease phenotype in heterozygotes of AD genes. Autosomal recessive diseases, on the other hand, comprise a majority of genetic diseases resulting mostly from deficient and/or defective production of proteins that act as enzymes rather than as structural proteins, e.g. inborn errors of metabolism. Enzyme dynamics allow for prolonged and sustained mediation of recurring metabolic reactions by small amounts of the enzyme, sometimes as low as 5% of the amount needed under normal physiological conditions. Hence, for an autosomal recessive (AR) disorder to be expressed in an affected patient, mutation of both parental genes is required, thus necessitating a heterozygous disease status of both parents, except for exceptional abnormal conditions like, for instance, uniparentaldisomy where both homologous chromosomes are inherited from the same parent.

Clinical Genetics

Clinical genetics implies the application of concepts of basic genetic knowledge in managing patients and carriers of genetic diseases [24,25]. The prime challenge in clinical genetics practice is to attain accurate diagnosis of the genetic disease. In many cases, the diagnosis might be straightforward due to pathognomonic clinical phenotypes, in others it can be confirmed via specific diagnostic investigations, e.g. cytogenetic studies for chromosomal abnormalities, mutation analysis for single gene disorders and biochemical assays for metabolic errors. Unfortunately, in much more cases, accurate diagnosis of genetic diseases represents a real challenge due to many factors headed by lack of sufficient information regarding the structure and functions of the human genome and human proteome. Proper diagnosis is not only important for defining effective therapeutic and/or prophylactic

Traditional patterns of inheritance	Non-traditional patterns of inheritance
1. Autosomal dominant inheritance	1. Inheritance of mitochondrial disorders
2. Autosomal recessive inheritance	2. Inheritance of chromosomal abnormalities
3. X-linked dominant inheritance	3. Inheritance of multifactorial diseases
4. X-linked recessive inheritance	4. Inheritance of triplet repeat expansion disorders
5. Y-linked inheritance	5. Uniparentaldisomy
	6. Inheritance of microdeletion/ microduplication defects
	7. Genetic imprinting
	8. Gonadal Mosaicism

Table 5: Patterns of inheritance of genetic disorders.

measures, but it is also crucial for offering accurate counseling advice to patients as well as to their concerned family members.

Clinical classification of genetic disorders delineates five major distinct disease categories: chromosomal aberrations, congenital malformations, in born errors of metabolism, mitochondrial disorders and systemic genetic syndromes, in addition to system-specific or organ-specific diseases affecting specific systems or individual organs, even specific cell lines, of the body. Within each of these categories, the defect might be sporadic affecting only the index case or it might be familiar when multiple family members are similarly affected with the disease. Isolated genetic defects refer to single tissue/organ/system affection without affection of any other parts, e.g. cardiomyopathy, retinitis pigmentosum or polydactyly. Conversely, systemic genetic disorders affect multiple organs/systems, e.g. Marfan syndrome. Chromosomal aberrations have, in most cases, widespread affection of many, sometimes most body parts due to involvement of large numbers of genes in their causation. The same applies also to most mitochondrial disorders and congenital malformations. However, some malformations are isolated anomalies affecting only single organ or localized part of the fetus, like the heart in isolated congenital heart disease. Similarly, multifactorial diseases caused by the mutational pathogenetic effect(s) of environmental teratogens on a susceptible genetic background might be isolated defects, e.g. pyloric stenosis and cleft lip or palate, or present with multiple organ/system affection like syndromes caused by teratogenic drugs and syndromes caused by intrauterine infections.

Clinical diagnosis of genetic diseases proceeds along the same traditional protocols followed in other medical specialties that comprise history taking, examination and diagnostic investigations. History taking is very important in clinical practice and nowhere is this illustrated more clearly than in clinical genetics. In many genetically-determined disorders like congenital malformations, history taking must be dated back to prenatal, sometimes to preconception or even to premarital history of the mother or of both parents. Other aspects of history crucial for establishment of proper diagnosis of many types of genetic diseases include perinatal, neonatal, developmental history and family history of similar or related diseases.

Laboratory diagnosis of genetic diseases is currently achieved through large panel of investigations. Some of these investigations are specific for genetically-determined disorders like cytogenetic investigations for chromosomal abnormalities, biochemical assays for inborn errors of metabolism and molecular mutation analysis for nuclear and mitochondrial single gene disorders. A large panel of conventional investigations complements classic genetic diagnostic approaches and represents an indispensable supplementary diagnostic techniques needed for detecting pathological defects associated with genetic diseases. These conventional diagnostic techniques include, for instance, radio-imaging and ultrasonographic studies, electro-physiological investigations, histopathological examinations, biochemical assays, and many others.

Treatment of genetic diseases aims primarily at alleviating sufferings of patients and avoiding development of complications. With the exception of surgically correctable congenital malformations, genetic diseases are considered as incurablein view of presence of the underlying inherited defect in all cells of the body. However, the wide spectrum of currently available therapeutic and prophylactic approaches can provide appreciable, sometimes effective, improvement for large numbers of patients affected with varying categories of genetic disorders. These effective management approaches comprise, mostly, conventional measures like drug therapy, nutritional manipulation,

enzyme replacement, organ transplantation and surgical intervention. Though genetic therapies for genetic diseases represent the ultimate hope of curing these defects, they are still in the experimental stage because of lack of comprehensive knowledge of the human genome. These genetic therapies include single gene therapy trials where a normal gene is intended to be inserted via viral vectors, or some other vectors, into the nuclear genome to replace deficient or defective function of a disease gene, and whole genome therapy trials like stem cell therapy. Other promising genetic therapies include myriads of approaches targeting all pathogenetic mechanisms and biomolecules involved in pathogenesis of genetic disorders, e.g. mRNA and micro RNA, translated and regulatory proteins, cell organelles, cell membranes and intercellular compartments. Examples of genetic therapies include use of interfering miRNA molecules or antisense oligonucleotides to suppress translation of harmful proteins, e.g. oncoproteins of tumor cells and the use of engineered chaperone proteins to correct some misfolding defects of translated proteins resulting from defective post-translation modifications of normally synthesized proteins. In fact, the list of newly invented therapeutic and alleviating measures for genetic disorders is continuously expanding quite rapidly, and it is hoped that gradual and complete cure of considerable proportion of genetic defects would be attained the more we know about the actual regulatory mechanisms that maintain the structural and functional integrity of the human genome. Prophylactic genetics represents a revolutionary approach in management of some types of genetic defects by preventing their occurrence through certain techniques, e.g. pre-implantation diagnosis, where carrier couples heterozygous for autosomal recessive single gene disorders are subjected to *in vitro* fertilization and mutation analysis of DNA extracted from one cell of each embryo followed by selection and intrauterine implantation of normal embryos only. Anticipation of possible health hazards, based on the genotype of patients/carriers or the family history, allows for implementing specific prophylactic measures to avoid expected complications and to alleviate possible consequences, and represents an essential aspect in management of patients with genetic diseases and carriers of mutant genes. This approach constitutes the cornerstone of prophylactic genetics. It also paves the way towards invention of effective prophylactic techniques based on detailed knowledge of the pathogenetic mechanisms and pathophysiological alterations underlying the development of genetic defects. The purposeful use of genetic knowledge and databases for prophylactic, diagnostic and therapeutic purposes, and in other related health and disease states, is a major achievement and represents the main framework of applied genetics. These applications include many important fields like genetic counseling, genetic screening (newborn screening and carrier screening), forensic genetics, genetic engineering, prenatal diagnosis, fetal therapy and genetic registries. Genetic registry databases, whether disease-specific or population-specific, represent essential requirements indispensable for many purposes, headed by their use in planning of health strategies aiming at establishing effective prophylactic measures and efficient diagnostic techniques for specific/common genetic disorders in populations, particularly closed or isolated populations with high rates of consanguineous marriages and increased prevalence of single gene disorders. Additionally, constructed genetic registry databases represent the main resources of plans aiming at elimination of certain lethal/disease genes from the gene pool of isolated populations. This approach represents one of the major concepts and prime aims of eugenics.

References

1. Hatzimanikatis V, Li C, Ionita JA, Broadbelt LJ (2004) Metabolic networks: enzyme function and metabolite structure. Curr Opin Struct Biol 14: 300-306.

2. Cheng J, Torkamani A, Peng Y, Jones TM, Lerner RA (2012) Plasma membrane associated transcription of cytoplasmic DNA. Proc Natl Acad Sci U S A 109: 10827-10831.

3. Li M, Wang IX, Li Y, Bruzel A, Richards AL, et al. (2011) Widespread RNA and DNA sequence differences in the human transcriptome. Science 333: 53-58.

4. Irwin H Herskowitz (1977) Principles of genetics. (2ndedn), Collier Macmillan International Editions.

5. Richardson JS (1981) The anatomy and taxonomy of protein structure. Adv Protein Chem 34: 167-339.

6. Balakirev ES, Ayala FJ (2003) Pseudogenes: are they "junk" or functional DNA? Annu Rev Genet 37: 123-151.

7. Glinsky GV (2009) Human genome connectivity code links disease-associated SNPs, microRNAs and pyknons. Cell Cycle 8: 925-930.

8. Kunarso G, Chia NY, Jeyakani J, Hwang C, Lu X, et al. (2010) Transposable elements have rewired the core regulatory network of human embryonic stem cells. Nat Genet 42: 631-634.

9. Rajski SR, Barton JK (2001) How different DNA-binding proteins affect long-range oxidative damage to DNA. Biochemistry 40: 5556-5564.

10. Morita R, Nakane S, Shimada A, Inoue M, Iino H, et al. (2010) Molecular mechanisms of the whole DNA repair system: a comparison of bacterial and eukaryotic systems. J Nucleic Acids 2010: 179594.

11. Gredilla R (2010) DNA damage and base excision repair in mitochondria and their role in aging. J Aging Res 2011: 257093.

12. Price DH, Gray MW (1998) Editing of tRNA. In: Modification and Editing of RNA. Grosjean H, Benne R (Eds.). ASM Press, Washington, DC pp: 289-306.

13. Pearl LH, Prodromou C (2006) Structure and mechanism of the Hsp90 molecular chaperone machinery. Annu Rev Biochem 75: 271-294.

14. Hartl FU, Bracher A, Hayer-Hartl M (2011) Molecular chaperones in protein folding and proteostasis. Nature 475: 324-332.

15. Malone CD, Hannon GJ (2009) Small RNAs as guardians of the genome. Cell 136: 656-668.

16. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, et al. (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84.

17. Douglas R Green (2010) Means to an End: Apoptosis and other cell death mechanisms. Cold Spring Harbor Laboratory Press.

18. Sliwinski T, Rozej W, Morawiec-Bajda A, Morawiec Z, Reiter R, et al. (2007) Protective action of melatonin against oxidative DNA damage: chemical inactivation versus base-excision repair. Mutat Res 634: 220-227.

19. Benjamin Pierce (2005) Genetics. A conceptual approach. (2ndedn), W.H. Freeman & company, Gordonsville, VA, USA.

20. Dale Jeremy, Park Simon F (2010) Molecular genetics of bacteria. (5thedn), John Wiley & Sons Ltd.

21. Griffiths JF (2007) Anthony Introduction to genetic analysis. 9th edition. W.H. Freeman & company, Gordonsville, VA, USA

22. Eberhard Passarge (2007) Color atlas of genetics. (3rdedn), Thieme Stuttgart, New York.

23. Jack J Pasternak (2005) An Introduction to Human Molecular Genetics: Mechanisms of Inherited Diseases. (2ndedn), John Wiley & Sons, Hoboken, NJ, USA

24. Rédei GP (2008) Encyclopedia of genetics, genomics, proteomics and informatics. (3rdedn), New Springer York, USA.

25. Watson James, Tania Baker, Stephen Bell, Alexander Gann, Michael Levine, et al. (2004) Molecular Biology of the Gene. (5thedn), Benjamin Cummings Menlo Park, California, USA.