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Basic concepts of medical genetics formal genetics, Part 3

Mohammad Saad Zaghloul Salem *

Faculty of Medicine, Ain-Shams University, Egypt

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9. Classification of genetic diseases

There is no single comprehensive and satisfactory approach for classification of genetic diseases in view of the too many parameters that have to be considered in this respect. Additionally, the need for accurate and final characterization of some aspects of these parameters can create marked overlap between different aspects used for classification. For example, **Marfan syndrome** can be classified **formally** as an autosomal dominant disease with a **clinical** spectrum including skeletal, ocular, and cardiovascular abnormalities. The main underlying **pathology** of the disease results from the synthesis of abnormal Fibrillin-1 protein leading to defective synthesis of connective tissue. Many **pathological** mechanisms contribute to the pathogenesis of the Marfan syndrome including inadequate sequestration of transforming growth factor beta (TGF-β) and deficient assembly/biogenesis and maintenance of the structural integrity of the framework of the elastic fibers, which constitutes a major component of the extracellular matrix. **Pathogenetic** defects in the Marfan syndrome involve abnormal synthesis, defective secretion, aberrant extracellular matrix utilization and post-translation modification defect leading to misfolding of Fibrillin-1 protein, thus rendering it ineffective for mediating its metabolic functions. Further analysis reveals that these defects are attributed to many **point mutations** (missense mutations and single nucleotide deletions) in the **Fibrillin 1 or FBN1 gene** on chromosome 15q21.1. Accordingly, accurate and proper characterization and classification of the Marfan syndrome, like most other genetic diseases, will have to take into consideration all these formal/clinical/pathological/pathogenetic and molecular aspects of the disease. However, a simple comprehensive approach defined by quantitative contribution of the genetic defect in causation of the disease seems more plausible and most useful in this regard for many reasons headed by availing accurate diagnostic and prognostic guidelines indispensable for providing proper management plans, including therapy and counseling advice, to affected individuals and their related family members. Relevant classification approaches to genetic diseases include the following approaches, that have to be conceived in view of the many overlaps between the multiple aspects of different parameters used for this scheme of categorizing and classification of genetic diseases. Table 6 summarizes classification based on molecular post-mutational defects in different stages of gene function, that constitute the bases of etiological classification of genetic disorders, Table 7 summarizes common, relatively comprehensive, classification approaches to genetic disorders, viz. etiological/pathological/formal and clinical classification, and Table 8 summarizes some common, currently defined pathogenetic mechanisms and pathophysiological alterations involved in pathogenesis of genetic disorders, which constitute the bases of pathological classification of these diseases.

(1) *Etiological classification:*

This approach is based on the nature/magnitude and type(s) of mutation(s) affecting the disease gene as well as on different pathogenetic mechanism(s) mediating the pathogenesis of the disease. Inclusion of the pathophysiological alterations that

* Tel.: +20 1225874345.
E-mail addresses: mszsalem@hotmail.com, mszsalem@yahoo.com
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Table 6 Post-mutational molecular mechanisms that disturb different stages of gene function.

1. Deletion of part of a gene, one or many genes, part of a chromosome, one or more chromosomes or even the whole genome
2. Rearrangement/instability of the genetic material
3. Damage/inaccessibility of promoter of the gene
4. Deficient/defective synthesis of transcription factors (microRNAs and nucleoproteins)
5. Deficient/defective transcription of mRNA
6. Deficient/defective post-transcriptional modifications of primary heterogeneous mRNA
7. Deficient/defective translation of mRNA leading to deficient/defective production of gene products
8. Deficient/defective post-translational structural modifications of synthesized proteins
9. Deficient/defective post-translational targeting/trafficking of synthesized proteins
10. Deficient/defective synthesis of regulatory signal transducing proteins/biomolecules
11. DNA repair defects
12. Damage to DNA-associated proteins
13. Defective synthesis of regulatory factors controlling cell division, intercellular contact, cell growth, etc
14. Defective regulation of transposon stability: spontaneous mutations and teratogenic malformations

directly underlie actual development of the various clinical/pathological abnormalities of the disease is important for final characterization of the disease in question. For example, Marfan syndrome can be etiologically characterized as a connective tissue disorder due to defective synthesis of Fibrillin-1 protein as a result of point mutations of the Marfan, or FBN1, gene. This detailed classification approach is crucial for accurate molecular diagnosis of the disease which is a prerequisite step for availing prenatal diagnosis, offering possible prenatal prophylactic and/or therapeutic interventions and provision of accurate counseling advice to concerned individuals.

(2) *Pathophysiological classification:*

Classification of genetic diseases according to the nature of the abnormal pathogenetic mechanism(s) that underlies pathogenesis of the disease is indispensable for understanding how the disease phenotype develops, how complications ensue and possible prognostic outcomes. More importantly, knowing how diseases develop and progress allows for hypothesizing, postulating and designing specific prophylactic and/or therapeutic approaches to combat pathogenesis of the disease, arrest its progression and alleviate much of the sufferings of affected patients.

The number of different pathogenetic mechanisms involved in the development of different categories of genetic disorders seems innumerable. This is attributed to the extreme complexity of the genetic regulatory processes exerted by the genome on the proteome responsible for mediation of every and all life activities in living cells. Gene function is a multistage process consisting of many consecutive and coherent steps, viz. gene activation/transcription/post-transcription modifications of mRNA/translation/post-translation modifications of synthesized proteins/trafficking and targeting of synthesized proteins to their cellular locations or extracellular destinations, and finally, suppression of transcription after synthesis of required amounts of the gene product. Multiple specific pathogenetic mechanisms have been identified for nearly every step of every stage of gene function. The list of pathogenetic mechanisms and pathophysiological alterations involved in, and responsible for, pathogenesis of genetic diseases comprises multitudes of diverse and interrelated mechanisms, as can be depicted in Table 8.

(3) *Formal classification:*

Formal classification of genetic disorders is determined by many parameters that can be deduced and depicted from extended family pedigrees constructed for affected patients and their family members. These parameters include the pattern(s) of inheritance, the nature of occurrence (sporadic versus familial), the heritability (heritable versus non-heritable) and inherited versus non-inherited newly acquired disorders due to fresh or de novo mutations in the zygote or in early embryonic cells. Formal classification of genetic diseases is mandatory for providing proper counseling advice to concerned individuals, as well as for providing guiding clues to proper diagnostic investigations relevant to the disease in question.

(4) *Clinical classification:*

This classification approach is defined by the specific, or pathognomonic, phenotype of affected individuals. It takes into consideration the nature of the disease whether it is an **isolated** (affecting one single tissue/organ or part of the body), a **pleiotropic** disorder with affection of many tissues/organs/many parts of the body due to the pleiotropic effects of the disease gene or a **syndromic** disorder presenting with affection of multiple related or unrelated tissues/organs or parts of the body.

As referred to previously, no single satisfactory approach exists for classification of genetic diseases. The following classification scheme, however, tries to combine as much of the different approaches as possible in order to simplify categorization, suggest diagnostic investigations and offer counseling advice to affected patients and their concerned family members.

9.1. Single gene disorders

Single gene disorders are caused by deleterious effects of single mutant genes. Nuclear single gene disorders are caused by genes located on chromosomes and inherited in a classical/traditional or Mendelian way. They comprise both autosomal disorders due to mutant genes located on the autosomes, chromosomes 1–22, and sex linked disorders caused by genes located on either the X chromosome, X-linked diseases, or on the Y chromosome, Y-linked diseases. Mitochondrial single gene disorders, as the name implies, are caused by mutant mitochondrial genes and have different patterns of non-classical/non-traditional or non-Mendelian inheritance. Mutant genes cause genetic disorders via one of three different and distinctive mechanisms, viz. synthesis of defective gene product, deficient synthesis of gene product or disturbed regulation of one or more physiological cellular activities. Though the exact number of genetic diseases is not known, because the list of disease genes is progressively expanding, the majority of currently defined genetic diseases are single nuclear autosomal gene defects. Additionally, nearly 70% of these defects are caused by point mutations of causative mutant genes.

Table 7 Classification of genetic disorders.

1. Etiological classification	**1. Nuclear gene mutations** a. Point mutations b. Small mutations c. Gross mutations d. Genomic mutations (Involving the whole genome): triploidy, tetraploidy **2. Mitochondrial gene mutations**
	1. Exclusive genetic disorders **a. Single gene disorders** **b. Polygenic disorders** 1. Few mutant genes 2. Chromosomal abnormalities a. Numerical abnormalities: trisomy, monosomy, hypodiploidy, heperdiploidy b. Structural abnormalities: deletion, translocation, inversion, chromosome breakage, isochromosome formation, ring chromosome formation. c. Microdeletion syndromes d. Microduplication syndromes e. Microtriplication syndromes f. Telomere region abnormalities **2. Multifactorial disorders (Environmental teratogen + susceptible genetic constitution).**
2. Pathophysiological classification	**A. Pathogenetic mechanisms** **B. Pathophysiological alterations**
3. Formal classification	**A. Pattern of inheritance** **1. Mendelian/classic/traditional patterns** a. Autosomal dominant b. Autosomal recessive c. X-liked dominant d. X-linked recessive e. Y-linked f. Co-dominant inheritance. **2. Non-Mendelian/non-classic/non-traditional patterns** a. Genic imprinting b. Genomic imprinting c. Di-, Tri-, Tetra-, Penta-, Hexa-triplet expansion defects d. Uniparental disomy (Isodizomy/Heterodisomy) e. Mitochondrial inheritance f. Germ line (gonadal) mosaicism g. Micro deletion/duplication/triplication disorders h. Multifactorial disorders. **B. Pattern of occurrence** 1. Sporadic (only case in the family) 2. Familial (many similar cases in the family). **C. Heritable and non-heritable disorders.** **D. Inherited and acquired disorders.**
4. Clinical classification	**1. Isolated disorders:** affection of single organ, tissue, part of the body **2. Pleiotropic disorders:** affection of many tissues, organs, parts of the body **3. Syndromic disorders:** affection of multiple related or unrelated parts

9.2. Polygenic disorders

Polygenic disorders result from combined defects in many mutant genes. The co-participation of either different or functionally related genes in pathogenesis of clinically distinctive polygenic disease phenotypes can be interpreted in view of the mediation of all metabolic networks in the cell by large numbers of proteins and enzymes synthesized under direct control of structural genes. Accordingly, development of polygenic diseases caused by pathophysiological disturbances in one or more of these networks requires defective or deficient functions of many genes responsible for regulating these networks. The list of polygenic diseases comprises large numbers of diseases, some of which are of major health concern, e.g. hypertension, coronary heart disease, diabetes mellitus, bronchial asthma, epilepsy, many types of common cancers, schizophrenia and manic depressive psychosis.

9.2.1. Chromosomal aberrations

Chromosomal aberrations constitute an important category of polygenic disorders caused by defects affecting large numbers, sometimes tens to hundreds, of different separate as well as of functionally related genes. This particular category of genetic disorders might be caused by different pathogenetic mechanisms including **structural** defects e.g. terminal/interstitial deletions, duplications, insertions, unidirectional/mutual translocations, isochromosome formation, pericentric/paracentric inversions, and many others, and **numerical** aberrations like trisomy, monosomy, hypodiploidy and hyperdiploidy.

9.2.2. Microdeletion syndromes, contiguous gene syndromes or segmental aneusomy (Table 9)

Microdeletion syndromes, contiguous gene syndromes or segmental aneusomy (Table 9), constitute an important

subcategory of chromosomal abnormalities that involve the deletion of a minute segment including multiple contiguous genes on a localized region of a chromosome. These syndromes are characterized by distinctive recognizable clinical phenotypes with wide spectra of heterogeneous pleiotropic manifestations. Though the pleiotropic phenotype of a contiguous gene syndrome can be caused by the deletion of a specific pleiotropic gene whose product is participating in mediating multiple functions, it can be due to the deletion of a number of tightly linked contiguous genes cooperatively participating in mediating specific functions, i.e. functionally related genes.

Table 8 Common pathogenetic/pathophysiological mechanisms of genetic diseases.

1. Loss/damage/duplication/inactivation of nuclear genes
2. Mutation of mitochondrial genes (mitDNA): mitochondrial disorders
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/editing
9. Deficient/defective post-transcription modifications of mRNA
10. Deficient translation of proteins
11. Translation of structurally 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 cell cytoskeleton
22. Imprinting defects: genomic imprinting disorders and genic imprinting diseases
23. Deficient/defective regulation of cellular functions: signal transduction defects
24. Deficient/defective transport across cell membranes: transport defects
25. Deficient/defective transport across cell pores: chanellopathies
26. Deficient/defective secretion of gene products: protein/enzyme deficiency disorders
27. Deficient/defective catabolism of metabolic waste products: storage disorders
28. Deficient/defective positioning of structural proteins: cell cytoskeleton disorders
29. Deficient/defective regulation of intracellular metabolic networking
30. Deficient/defective production of cellular energy: oxidative-phosphorylation disorders
31. Ubiquitination/proteasome degradation defects
32. Apoptosis defects
33. Defective regulation of ciliary movements: ciliary dyskinesia disorders
34. Defective synthesis of nuclear envelope: laminopathies/nuclear envelopathies
35. Defective regulation of embryonic/fetal development: congenital malformations

Due to paucity of information as regards the underlying pathogenetic mechanisms responsible for the development of microdeletion syndromes, it is often not possible to decide whether a specific syndrome phenotype is caused by deficient/defective synthesis of a product secondary to deletion of one single gene or by deficient/defective synthesis of many products secondary to concurrent deletions of multiple genes at the microdeletion region.

Many observations suggest that possible etiological relationships might exist between microdeletion-inducing mechanism(s) and imprinting. For instance, 5–10% of cases with neurofibromatosis 1 (NF 1) are caused by microdeletions in the q11.2 region of chromosome 17 (17q11.2) and about 80% of these cases are due to microdeletions of **maternal** origin due to unequal crossing over in maternal meiosis 1 [1]. Also, cases with Sotos syndrome have been found to have a preferential **paternal** origin of microdeletions caused by prezygotic chromosome or chromatid rearrangements [2]. Similarly, parental origin effect in a classic form of Cockayne syndrome due to a de novo microdeletion of maternal origin spanning the ERCC6 gene was detected [3]. Other relevant findings pointing to a possible relationship between imprinting and microdeletion include the detection of a novel microdeletion in the IGF2/H19 imprinting control center that defines a recurrent mutation mechanism in familial Beckwith–Wiedemann syndrome [4] and the participation of both mechanisms independently in pathogenesis of cases of Prader–Willi syndrome. However, these findings might reveal a possible relationship between imprinting and over dosage states of microduplication and microtriplication rather than with haplo-insufficiency states like microdeletion syndromes. In view of the, still, undefined biological significance of imprinting and the poorly defined mechanisms of this critical phenomenon which plays a major role in normal embryonic/fetal development in mammals as well as in other non-mammal species, imprinting can be looked at as an important potential genomic regulatory mechanism aiming at controlling genomic overdose imbalances that are prone to happen due to massive genetic over expression during critical periods of embryonic and fetal development. Defective genomic regulation of imprinting control centers might result in faulty expression and persistence of the defect(s) all through post-natal life. This assumption makes it quite feasible to hypothesize that imprinting disorders could be considered as sex-determined, autosomal or X-linked/Y-linked, dominant disorders consider in view of their particular pattern of occurrence. A perplexing concept in this regard is the assumption that genetic imprints acquired during parental gametogenesis are maintained during pre-implantation development when reprogramming of the overall genome occurs [5], since there is neither a need nor a significance of overall genome reprogramming. There is no evidence in support of this assumption. Also, none of the regulatory mechanisms responsible for genome reprogramming have been defined, or even postulated.

However, a lot of research is needed in order to reveal the real biological significance and exact molecular mechanisms of both phenomena of genic and genomic imprinting.

9.2.3. Microduplication syndromes

Microduplication syndromes another subcategory of minute structural chromosomal abnormalities, are caused by duplica-

Table 9 Microdeletion syndromes.

Syndrome	Phenotypic features	Cytogenetic location
Prader–Willi syndrome	Hypotonia, hyperphagia, obesity, short stature, small hands and feet, hypopigmentation, mental retardation	15qll-ql3
Angelman syndrome	Hypotonia, microcephaly, ataxic gait, inappropriate laughter, seizures, hypopigmentation, mental retardation	15qll-ql3
Williams syndrome	Dysmorphic facies, infantile hypercalcemia, congenital heart disease, gregarious personality, premature aging of the skin, mental retardation	7qll.23
Miller–Dieker syndrome	Type I lissencephaly, dysmorphic facies	17pl3.3
Velo-Cardio Facial syndrome (Del-22q)	Abnormal facies, cleft palate, thymic hypoplasia, hypocalcemia, heart defect (conotruncal defect)	22qll
Langer-Giedion syndrome	Tricho-rhino-phalangeal Syndrome (sparse hair, bulbous nose, cone-shaped phalangeal epiphyses), multiple exostoses, mental retardation	8q24.1
Rubinstein–-Taybi syndrome	Dysmorphic facies, broad thumbs and first toes, mental retardation	16pl3.3
Alpha-thalassemia and mental retardation (ATR-16) syndrome	Dysmorphic facies, alpha-thalassemia, mental retardation	16pl3.3
Alagille syndrome	Dysmorphic facies, chronic cholestasis, vertebral arch defects, pulmonic stenosis	20pll.23-pl2.2
Albrights hereditary osteodystrophy-like syndrome	Short stocky build, abnormal facies, developmental delay, brachy-meta-phalangism, seizures	2q37
AWTA (WAGR) syndrome	Aniridia, Wilms Tumor, genitourinary dysplasia, mental retardation	11pl3
Smith–Magenis syndrome	Dysmorphic facies, behavioral abnormalities, self destructive behavior, peripheral neuropathy, mental retardation	17p11.2 (FLII, TOP3, SHMT1)
Greig-Cephalopoly-syndactyly syndrome	Craniosynostosis, polysyndactyly, mental retardation	7pl3
Cat-Eye syndrome	Coloboma, choanal atresia, learning disabilities, mental retardation	22qll.2
Diamond–-Blackfan syndrome	Red blood cell hypoplasia, macrocephaly, hypotonia and psychomotor retardation	19ql3.2
van der Woude syndrome	Cleft Lip With or Without Cleft Palate; Bilateral Lip Pits; Hypodontia	1q32-lq1
NF1 Microdeletion syndrome	Neurofibromatosis, early onset of cutaneous neurofibromas, facial dysmorphism, learning disabilities, mental retardation	17qll.2
Y chromosome micro–deletion syndrome	Unilateral cryptorchidism, idiopathic infertility	Yql3
Distal 22q microdeletion	Hypotonia, severe language delay, mild facial dysmorphism	22ql3-22qter
Xp21 Deletion	Muscular dystrophy, glycerol kinase deficiency, congenital adrenal hypoplasia, mental retardation	Xp21
1p36 Deletion syndrome	Hypotonia, developmental delay, growth abnormalities, craniofacial dysmorphism, minor cardiac malformations	1p36
Saethre–Chotzen syndrome	Learning difficulties, short stature, craniosynostosis, eyelid anomalies, limb anomalies, breast cancer.	7p21.1
Retinoblastoma		10q26.13
		13q14

tions of minute chromosomal segments comprising multiple contiguous genes. Similar to microdeletion syndromes, many microduplication syndromes with specific recognizable phenotypes have been defined (Table 10).

9.2.4. Microtriplication syndromes

Microtriplication syndromes due to triplication of minute chromosomal segments may emerge as a new category of structural chromosomal aberrations. Currently, few microtriplication syndromes caused by this pathogenetic mechanism have been identified, e.g. microtriplication involving the Williams–Beuren region at (7q11.23) with clinical features similar to, but more severe than, those observed in patients with a duplication of this region [6] and microtriplication of region (11q24.1) presenting a distinctive phenotype with short stature, characteristic facial features, keratoconus, overweight and intellectual disability [7].

Submicroscopic chromosomal abnormalities detectable as microdeletions/microduplications/microtriplications represent localized genomic rearrangements. Though genetic microduplications/microtriplications might be looked at as compensatory genomic events with assumed beneficial advantage in

Table 10 Microduplication syndromes.

Syndrome	Clinical features	Cytogenetic location
Neonatal epilepsy microduplication syndrome		2q24.2-q24.3
Parkinson disease 1		4q22.1
Adult-onset autosomal dominant leukodystrophy	Autonomic abnormalities (postural hypotension, neurogenic bladder, and rectal incontinence), pyramidal and cerebellar dysfunction, symmetric demyelination of the CNS.	5q23.2
Pseudo trisomy 13 syndrome	Holoprosencephaly, postaxial polydactyly, cardiac defects, genital anomalies, facial dysmorphism.	5q35.1
Transient neonatal diabetes mellitus	Insulin-requiring hyperglycemia within the first month of life, most cases resolve at age of 3 months, the rest have a permanent form of diabetes type II.	6q24.2
Parkinson disease 2		6q26
Chondroma		6q27
Williams-Beuren region duplication syndrome	Facial dysmorphism, psychomotor and developmental delay, severe impairment in expressive language, epilepsy.	7q11.23
Beckwith–Wiedemann syndrome		11p15
Charcot-Marie-Tooth Type 1A		17p11.2
Potocki–Lupski syndrome	Autism, mental retardation, attention-deficit disorder, obsessive-compulsive behavior, infantile hypotonia, cardiac malformations, short stature	17p11.2
Triphalangeal thumb polysyndactyly syndrome		7q36.3
Split-hand/foot malformation 3		10q24.32
Silver-Russell syndrome		11p15.5
Spinocerebellar ataxia type 20		11q12.2q12.3
Miller–Dieker microduplication syndrome		17p13.3
Charcot-Marie-Tooth Type 1A		17p12
Neurofibromatosis 1		17q11
Sotos-like syndrome		19p13.2
Down syndrome/DS		21q22.13
Cat-Eye microduplication syndrome		22p11.1-q11.21
Pelizaeus–Merzbacher microduplication (X-linked recessive hypomyelinative leukodystrophy)	Spasticity of the legs and later the arms, cerebellar ataxia, dementia, parkinsonian symptoms.	Xq22.2
17-beta-hydroxysteroid dehydrogenase	Neurologic abnormalities, including psychomotor retardation and loss of mental and motor skills	Xp11.22
X-linked hypopituitarism	Neonatal hypoglycemia, short stature, variable deficiencies of other pituitary hormones, normal mentality	Xq27.1

cases of genomic losses or stresses, they result in disease phenotypes, sometimes more severe than corresponding deletion phenotypes. The devastating intellectual disability that characterizes the large majority of these diseases makes affected patients incapable of reproduction with no chances of transmitting the disease. They are examples of neither inherited nor heritable genetic diseases. The persistent de novo occurrence of these genetic defects reveals a different pathogenetic mechanism that, still, has no clear interpretation. The presence of different contiguous, mostly functionally unrelated, gene clusters at locations of these defects might reflect failure of attaining optimal genomic integrity in view of the wide intergenic, seemingly functionless, segments of the genome. Though gene clustering, especially in genomes of primitive organisms, might be considered as an effective genetic economy mechanism whereby fewer common transcription factors are needed to activate large number of genes, defective or deficient synthesis of these common factors may lead to multiple genetic defects of involved clusters. Genetic clustering in large, more complex genomes, however, has no satisfactory explanation yet.

9.3. Multifactorial disorders

Multifactorial genetic disorders refer to diseases caused by combined actions of both an environmental factor and a genetic component. Pathogenesis of multifactorial diseases is attributed to the deleterious actions exerted by the environmental factor, or mutagen, on a susceptible genetic background. The spectrum of these diseases is very wide in view of the very early exposure of the zygote and descendant cells to multitudes of intra-uterine and extra-uterine environmental effectors that persist all through stages of embryonic and fetal

development till birth, and get intensified all through post-natal life till death. Accordingly, multifactorial diseases can develop during intra-uterine development in view of embryonic/fetal susceptibility to deleterious effects of mutagenic factors, particularly teratogenic mutagens, where they make their appearance and present as **congenital multifactorial diseases**, e.g. congenital malformations. Similarly, multifactorial diseases can develop at any time during post-natal life as consequences of somatic mutations imposed by the persistent and everlasting every day exposure of human cells to the environmental mutagens, viz. carcinogens/clastogens/non-specific mutagens, present everywhere in our environment. Common examples of **acquired multifactorial diseases** include non-hereditary cancers, immunodeficiency disorders, coronary heart disease, hypertension, diabetes mellitus, schizophrenia, peptic ulcer disease, tuberculosis, psoriasis and many others.

In this respect, genetic diseases can be classified into **purely genetic disorders** solely caused by mutant genes without any participation of any environmental factors in their development, like Duchenne myopathy, achondroplasia, hemophilia, neurofibromatosis, Down syndrome and Marfan syndrome, and **multifactorial diseases** where the pathogenetic effects of an environmental mutagen are necessary for development and progression of the disease. The impact of the genetic susceptibility to environmental factors varies widely as regards its nature, sex of susceptible individual and magnitude of the genetic deviation from normal status. The nature of the genetic deviation determines to a large extent the susceptibility to and the possibility of developing a multifactorial disease.

Genetic deviations comprising subtle defects in DNA repair mechanisms or mild incompetence of the immune system are expected to progress to drastic pathological conditions, e.g. cancer and immunodeficiency, upon being sufficiently stressed by potent environmental mutagens, than other genetic deviations involving less important or non-critical aspects of genetic functions. For these reasons, multi-factorial disorders vary widely as regards their rates of occurrence, sex predilection, ethnic distribution, age of onset, phenotypic spectrum and prognostic outcomes. However, the mere presence of susceptible individual genetic constitution does not dictate indispensable development of the disease unless pathogenetic exposure of specific targeted cells to the effects of the proper mutagen in a sufficient dose at a critical time occurs.

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Additional resources

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