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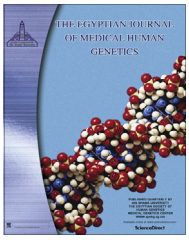

EDUCATIONAL CORNER OF THE ISSUE

Basic concepts of medical genetics. Formal genetics, part 4

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Non-traditional patterns of inheritance

Non-traditional/non-classical/non-Mendelian patterns of inheritance refer to different modes of transmission of genetic diseases that are not caused by single mutant genes. These diseases include a wide variety of genetically-determined disorders, e.g., polygenic diseases/chromosomal aberrations/mitochondrial disorders and multifactorial diseases. Non-traditional inheritance patterns are not compatible with the rules of inheritance that characterize the transmission of single gene disorders since they differ from each other in many respects like rates of occurrence, recurrence risk, sex predilection, spectrum of phenotypic variation and many others. The characteristics of these non-traditional patterns are dependent solely on the nature of the disease as regards its etiology and the specific pathogenetic mechanism(s) underlying its development. Recognition of these different inheritance patterns is important for the provision of proper counseling advice because they have different recurrence risks and different clinical and management implications. Non-traditional patterns of inheritance characterize diseases caused by specific pathogenetic mechanisms that include: defective genetic imprinting, uniparental disomy, nucleotide repeat expansion (tri/tetra/penta/hexa-nucleotide repeat expansion), mutations of mitochondrial genome, mutations caused by combined multifactorial (genetic/environmental) effects, mosaicism, chromosomal aberrations, microdeletion/microduplication/microtriplication defects and polygenic defects [1] (Table 1).

1. Genetic imprinting

Genetic imprinting refers to the predetermined functional status of a gene, a group of genes, part or most of a chromosome. This imprint might be imposed by different factors. For instance, it might be imposed by the parental origin, i.e. specific genes or sets of genes transmitted by the mother or the father may be expressed or suppressed according to their parent of origin, thus resulting in a specific monoallelic gene expression profile. This type of imprinting might be referred to as **parental imprinting** [2]. Alternatively, a gene might be silenced/suppressed/turned off or kept functioning following the completion of the critical stages of embryogenesis/differentiation/growth and development of the offspring. This type of imprinting might be referred to as **temporal imprinting**. A third type of imprinting that might be referred to as **spatial imprinting** is determined by the location of the gene, where a gene is suppressed or activated by regulatory mechanisms imposed by adjacent chromatin modifications (Table 2).

In diploid organisms, somatic cells possess two copies of the genome and each autosomal gene is represented by two copies, or alleles, with one copy inherited from each parent at fertilization. For the vast majority of autosomal genes, expression occurs from both alleles simultaneously. In mammals, however, a small proportion (<1%) of genes are parentally imprinted, meaning that gene expression occurs from only one allele. The expressed allele is dependent upon its parental origin. For example, the gene encoding Insulin-like growth factor 2 (IGF2/Igf2) is only expressed from the allele inherited from the father [3].

Imprinting is a fundamental genomic regulatory mechanism during development and differentiation whereby overexpression of specific sets of maternal or paternal genes and silencing of other sets of maternal or paternal genes is mandatory for

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Table 1 Pathogenetic mechanisms underlying non-traditional inheritance patterns.

1. Defective genetic imprinting
2. Uniparental disomy
3. Nucleotide repeat expansion (tri/tetra/penta/hexa-nucleotide repeat expansion)
4. Mutations of mitochondrial genome
5. Mutations caused by combined multifactorial (genetic/environmental) effects
6. Mosaicism
7. Chromosomal aberrations
8. Microdeletion/microduplication/microtriplication defects
9. Polygenic defects

ensuring proper growth, differentiation and specialization of embryonic and fetal tissues and organs. This specific pattern of genetic imprinting inherited from both parents is maintained in somatic cells of the offspring all through the postnatal life. However, if genomic regulation over this default specific expression/suppression profile is lost or disturbed due to mutational events, defective imprinting results. Suppression or silencing of maternal or paternal genes that are normally active in their normal condition will result in functional deficiency of their product(s). Similarly, overexpression of genes that are kept silenced after differentiation and specialization, or that function within their programed scale, will result in re-transcription/re-synthesis of their products. In either condition, perturbation of the strict functional balance between the three major components of the genetic material of the cell, the genome/the transcriptome/the proteome, occurs leading to the development of imprinting defects and pathogenesis of imprinting disorders.

The exact pathogenetic mechanisms underlying the development of imprinting defects are neither clear nor completely understood up till now, though many epigenetic alterations of the genome, including methylation/demethylation of DNA and chromatin modifications have been proposed as factors implicated in imprinting. Pathogenesis of genetic disorders due to imprinting happen when individuals having suppressed or silenced imprinted genes, thus behaving like functional carriers or heterozygotes, develop mutational defect of the other normal allele thus turning them into diseased homozygotes. On the other hand, large numbers of genes are known to control and regulate different aspects of post-fertilization processes and promote the exceedingly accelerated rates of growth and proliferation of embryonic and fetal cells. As the need for these genes diminishes markedly after that period, these genes are turned off and kept suppressed. Defects in maintaining the suppressed imprinting status of these genes leading to their reactivation might offer another plausible hypothesis to explain pathogenetic mechanisms underlying the development of genetic diseases resulting because of overexpression of temporally suppressed imprinted genes, like cancer.

In parental imprinting, a gene behaves differently depending on whether it is inherited from the father or from the mother. Genomic imprinting occurs when a gene or chromosome contributed by the mother differs functionally from a structurally identical gene or chromosome contributed by the father. There are a number of human disorders in which the clinical manifestations depend on the sex of the transmitting parent. For instance, the severe congenital form of myotonic dystrophy is maternally transmitted and nearly 10–20% of her offspring who inherit the disorder will manifest this severe form. In the Prader–Willi syndrome, a gene product needed for normal development, normally expressed only by the paternal allele, is missing. The disease phenotype results because the maternal allele of the gene is normally suppressed, thus affected offspring behaves like homozygous affected individuals. Approximately, 60–65% of individuals with the Prader–Willi syndrome are missing the gene due to its deletion from the paternal chromosome number 15. Additionally, unimaternal disomy for chromosome number 15, in which the child inherits both copies of chromosome number 15 from their mother and none from the father, account for about 30% of the cases. The reverse situation is met with in the Angelman syndrome caused by similar pathogenetic mechanisms leading to the functional absence of the gene when it is inherited from the mother, where the disease phenotype results because the paternal allele of the gene is normally suppressed.

2. Uniparental disomy (UPD)

Uniparental disomy is a rare cytogenetic abnormality. It occurs when both copies of a chromosome, or parts of a chromosome,

Table 2 Imprinting disorders.

Disorder	Pathogenetic mechanism
Prader–Willi syndrome	Paternal inheritance of the deletion of the chromosomal region 15q11-13 (band 11 of the long arm of chromosome 15) containing the paternally expressed genes (SNRPN and NDN)
Angelman syndrome	Maternal inheritance of the deletion of the chromosomal region 15q11-13 (band 11 of the long arm of chromosome 15) containing the paternally expressed genes (SNRPN and NDN)
Beckwith–Wiedemann syndrome	1. overactivity of the IGF-2 gene (growth factor) on the short arm of chromosome 11, 11p15 2. Suppressed or deleted copy of CDKN1C Cyclin-dependent kinase inhibitor 1C gene (inhibitor of cell proliferation) 3. KCNQ1OT1KCNQ1 gene; overlapping transcript 1 causing the *Beckwith–Wiedemann syndrome due to 11p15 microdeletion*
Silver–Russell syndrome	Hypomethylation of *H19* and *IGF2 genes* Maternal uniparental disomy (UPD) of chromosome 7
Pseudohypoparathyroidism	
Transient neonatal diabetes mellitus	1. Unipaternal disomy of gene(s) on chromosome 7 2. Imprinting of genes on chromosome 6
Ovarian and breast cancers (41% of cases)	Loss of the expression of the tumor suppressor gene NOEY2 [51]

are derived from one parent only. There is a preponderance of maternal versus paternal UPD; approximately 3:1. This rare event might be caused by different pathogenetic mechanisms happening during the formation of egg or sperm cells or during early stages of development. A disomic germ cell, sperm or ovum, with two allelic chromosomes resulting due to faulty meiotic nondisjunction, might participate in fertilization followed by loss of the allelic chromosome from the other germ cell, thus leading to the formation of a zygote with two allelic chromosomes transmitted from one parent only. This mechanism is thought to be the major cause of this cytogenetic abnormality. If nondisjunction affects a chromosome carrying a recessive mutant gene, the resulting disomic germ cell will have two chromosomes with two mutant genes. If the normal allelic chromosome from the other parent is lost in the immediate post-fertilization division, the zygote will have two mutant homozygous genes leading to the development of a recessive genetic disease. Alternatively, if one of the mutant chromosomes is lost, the resulting offspring will develop as a carrier or a heterozygote individual with no clinical consequences. Other less common, rare causes can lead to uniparental disomy, e.g., duplication of chromosomes or mitotic nondisjunction with selective loss of the other allelic chromosome in the immediate postfertilization stages. Uniparental disomy occurring late after fertilization might result in mosaicism in the placenta or even in parts of fetal tissues. The clinical phenotype of genetic diseases resulting from uniparental disomy varies widely depending upon the parental source of the disomic chromosomes, like the case in Prader–Willi and Angelman syndromes.

There are different cytogenetic types of uniparental disomies: 1. **Heterodisomy** in which a pair of non-identical chromosomes is inherited from one parent due to an error in earlier stages meiosis I during germ cell formation. 2. **Isodisomy** in which a single chromosome from one parent is duplicated due to an error in later stages meiosis II or due to postzygotic chromosomal duplication. Heterodisomy is essentially a benign condition and cases having it do not suffer phenotypical anomalies. On the other hand, if isodisomy affects a chromosome carrying a mutant gene from a carrier parent, the resulting offspring will manifest a recessive genetic disease, although one of the parents is normal. Accordingly, UPD should be suspected in cases manifesting recessive disorders, where only one parent is a carrier. An unexpected inheritance pattern where a couple of a normal parent and a homozygous affected parent gets normal offspring, due to unipaternal disomy of the chromosome carrying the gene in question, should also raise the suspicion of this cytogenetic error. Other aberrant inheritance situations that might result from uniparental disomy include homozygosity of autosomal recessive gene mutations, homozygosity of X-chromosomal disorders in females and father-to-son transmission of X-linked traits.

Another potentially hazardous pathogenetic consequence due to UPD resulting in phenotypical anomalies can be caused by uniparental inheritance of imprinted genes. If the disomic chromosomes happen to carry the mutant gene, then the affected offspring will behave as a homozygous individual and will have a genetic disease due to the total absence of gene product(s). Clinical phenotypes amenable for interpretation by these mechanisms include: the Prader–Willi syndrome and the Angelman syndrome that can be caused by UPD, or other errors in imprinting, involving genes on the long arm of chromosome 15 and the Beckwith–Wiedemann syndrome due to UPD of imprinted genes on the short arm of chromosome 11.

A peculiar cytogenetic abnormality caused by the inheritance of all chromosomes from one parent only is referred to as **uniparental diploidy**. Several pathogenetic mechanisms might cause this exceptional cytogenetic error including fertilization of an ovum by two sperms, post-fertilization duplication of a single sperm genome with selective exclusion of the genome of the ovum, total exclusion of sperm genome and duplication of the genome of the ovum or amalgamation of the genome of both the ovum and the polar body. These rare events represent instances of whole genomic imprinting where the whole maternal or paternal genome gets suppressed. These rare abnormalities are incompatible with normal developments, rather they lead to the formation of defective fertilization outcomes like hydatidiform moles, dermoid cysts and choriocarcinoma.

3. Nucleotide repeat expansion

Abnormal expansion of varying numbers of adjacent nucleotides of a functional gene, upon duplication of the gene during the DNA replication stage of the cell cycle, is a specific type of mutational events that lead to the construction of an abnormally large number of nucleotide repeats within the newly replicating gene. The gene becomes structurally abnormal, and if these expansion defects affect critical segments of the gene, deficient synthesis of gene products; mRNA/microRNA or proteins, or synthesis of abnormal defective/unstable gene products happen leading to the pathogenesis of genetic disorders. Nucleotide repeats normally exist along most genes in predefined numbers. Defective expansions and abnormal increase in these numbers disrupt the structural integrity of the gene and result in consequent functional deterioration due to resulting defects in synthesis of the gene product(s).

Nucleotide repeat expansion can involve varying numbers of adjacent nucleotides, e.g., di-, tri-, tetra-, penta- and hexanucleotide repeat expansion. Many molecular mechanisms have been postulated to be implicated in the pathogenesis of this specific mutation including defective DNA replication, fragment ligation and proofreading errors. Uncommon structural configurations of DNA during replication might also predispose to this pathogenetic defect [4].

Nucleotide repeat expansion is characterized by a progressive attitude. As the condition passes from one generation to the next in a given family, the repeat sequence is amplified causing more structural damage and more functional deterioration of the gene, thus causing an earlier appearance and an increase in the severity of clinical manifestation in successive generations, where greater the number of repeats occur along the gene, the more severe are the clinical manifestations of the disease This pathogenetic mechanism underlies the phenomenon of genetic **anticipation**. Anticipation disorders frequently involve repeating or expansion of three adjacent nucleotides (triplet repeat expansion). A long, ever expanding, list of genetic disorders caused by this nucleotide repeat expansion pathogenetic mechanism is delineated, most of them are due to the expansion of adjacent triplets, three nucleotides, hence referred to as triplet repeat expansion diseases. These disorders have widely varying clinical phenotypes depending on many factors including the specific nucleotide repeat, the

size of the repeat expansion and the functional role(s) of the gene product(s).

In over half of these disorders, the repeated codon or triplet, **CAG** (**C**ytosine-**A**denine-**G**uanine), codes for glutamine amino acid resulting in the synthesis of a polyglutamine segment, or tract, in the resulting protein. These diseases are commonly referred to as **polyglutamine diseases**. In the remaining disorders, the repeated codons do not code for glutamine and are classified as **non-polyglutamine** diseases (Tables 3 & 4).

4. Mitochondrial inheritance

The exclusive presence of mitochondria in the ovum, but not in the sperm, imparts to genetic diseases caused by mutations of mitochondrial genes specific non-mendelian inheritance patterns. Furthermore, oxidative-phosphorylation networks responsible for the ATP production in the mitochondria are mediated by proteins and enzymes synthesized by both mitochondrial and nuclear genes. Due to the maternal origin of mitDNA, mitochondrial mutations/disorders are inherited from the mother. In mitochondrial inheritance, a woman who carries a mutant mitochondrial gene passes the mutant gene to all her offspring and her daughters will pass the mutated mitochondria to their children. However, her sons will not transmit the disease to any of their children because sperm mitochondria do not participate in fertilization and zygote formation. Examples of genetic diseases manifesting this specific inheritance pattern because of mitochondrial gene mutations include Leber's hereditary optic neuropathy (LHON), the Wolff-Parkinson-White syndrome, Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP), Leigh's neuropathy-encephalopathy syndrome, the Myoclonic Epilepsy and Ragged Red Fibers syndrome (MERRF), Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), Diabetes mellitus and deafness (DAD), the **Kearns–Sayre syndrome (KSS),** the Pearson **syndrome** and many others.

Mutations in mitochondrial genes can be diagnosed by the molecular mutation analysis of mitochondrial gene. The list of mitochondrial diseases is progressively increasing and comprises endless numbers of genetic defects/disorders due to the central roles mediated by the mitochondria in ATP and energy production in the cell. Additionally, mitochondria conduct many other critical metabolic and regulatory roles in the cell including mediation and regulation of urea cycle reactions, regulation of apoptosis, cell aging, fatty acid metabolism, glycolysis pathways in stressful condition, storage of calcium ions and regulation of calcium homeostasis, synthesis of heme, synthesis of steroids, and many others.

Table 3 Polyglutamine (CAG) triplet repeat expansion diseases.

Disease	Mutant gene	Normal number of repeats	Pathogenic number of repeats
HD (Huntington's disease)	HTT (Huntingtin)	6–35	36–250
SBMA (Spinobulbar muscular atrophy or Kennedy disease)	Androgen receptor on the X chromosome	9–36	38–62
SCA1 (Spinocerebellar ataxia Type 1)	ATXN1	6–35	49–88
SCA2 (Spinocerebellar ataxia Type 2)	ATXN2	14–32	33–77
SCA3 (Spinocerebellar ataxia Type 3 or Machado–Joseph disease)	ATXN3	12–40	55–86
SCA6 (Spinocerebellar ataxia Type 6)	CACNA1A	4–18	21–30
SCA7 (Spinocerebellar ataxia Type 7)	ATXN7	7–17	38–120
SCA17 (Spinocerebellar ataxia Type 17)	TBP	25–42	47–63
DRPLA (Dentatorubropallidoluysian atrophy)	ATN1 or DRPLA	6–35	49–88

Table 4 Non-Polyglutamine triplet repeat expansion diseases.

Disease	Mutant gene	Expanding repeat	Normal number of repeats	Pathogenic number of repeats
FRAXA (fragile X syndrome)	*FMR1*, on the X-chromosome	**CGG**	6–53	230+
FXTAS (fragile X-associated tremor/ataxia syndrome)	*FMR1*, on the X-chromosome	**CGG**	6–53	55–200
DM (myotonic dystrophy)	DMPK	**CTG**	5–37	50+
FRDA (Friedreich's ataxia)	FXN or X25, (frataxin—reduced expression)	**GAA**	7–34	100+
FRAXE (Fragile XE mental retardation)	AFF2 or FMR2, on the X-chromosome	**CCG**	6–35	200+
SCA8 (Spinocerebellar ataxia type 8)	OSCA or SCA8	**CTG**	16–37	110–250
SCA12 (Spinocerebellar ataxia type 12)	PPP2R2B or SCA12	**nnn** On 5′ end	7–28	66–78

5. Multifactorial inheritance

Multifactorial, or complex, genetic disorders are 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 on the susceptible genetic background. The spectrum of these diseases is very wide in the view of the countless numbers of environmental factors capable of damaging the genetic constitution of humans, mutagens/teratogens/carcinogens/clastogens, and the exceedingly large numbers of mutant genes that make their bearers at a high susceptibility risk of suffering diseases upon exposure to an offending environmental trigger. 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 [5].

In view of the very early exposure of the zygote and descendant cells to multitudes of intra-uterine and extra-uterine environmental effectors that persists 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. Alternatively, multifactorial diseases can develop at any time during postnatal life as the 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.

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.

Neither the exact pathogenetic mechanisms nor the nature of the genetic component in multifactorial diseases are completely understood. Though a polygenic component has been postulated to be responsible for conferring genetic susceptibility in these diseases, none of the complete sets of genes related to specific complex multifactorial diseases have been defined. Accordingly, screening, early diagnosis or prophylactic approaches are not available for the majority of these diseases.

Table 5 Multifactorial or complex disorders.

Congenital malformations: cleft palate/lip, neural tube defects such as spina bifida
Cardiovascular diseases: high blood pressure, some causes of heart disease, high cholesterol
Neurological/psychiatric disorders: Alzheimer disease in later life, schizophrenia, bipolar disorder
Skin disorders: psoriasis, moles, eczema
Respiratory: asthma, allergies, emphysema
Muscular/skeletal diseases: arthritis, rheumatic disorders, osteoporosis
Metabolic disorders: diabetes
Malignant tumors: bowel, breast, ovarian, bowel, melanoma and prostate

The estimation of the occurrence or recurrence risk for developing a specific multifactorial disease in a particular family is largely speculative and is dependent on many factors including: sex of the index case, age at onset of clinical manifestations and the clinical course of the disease, closeness to affected individuals, number of affected cases in the family, ethnic background and many others. Provisional diagnosis of suspected multifactorial diseases rests on many clues that include undefined complex clinical phenotypes affecting many family members and transmitted in a pattern that do not conform with known rules of Mendelian inheritance. Failure to detect molecular/cytogenetic/biochemical abnormalities is an additional clue to suspect the multifactorial background of these diseases (Table 5).

6. Mosaicism

Mosaicism signifies the presence of two or more populations of cells with different genetic constitutions, or genotypes, of each in an individual who has developed from a single zygote. Various mechanisms underlie the development of this abnormal genetic condition. In the preimplantation embryonic stage, anaphase lag appears to be the main process by which mosaicism arises. Chromosomal non-disjunction and whole genome endoreduplication are other pathogenetic mechanisms that can lead to mosaicism. Post-fertilization mutational events propagated to a subset of descendant cells results in the mosaicism of varying tissues or parts of organs that develop from these cells in later stages of development. For instance, mosaic children with the Down syndrome have two cell lines, one normal with 46 chromosomes and another triploid cell population having 47 chromosomes. Also, about 50% of cases with the turner syndrome have mosaic genetic constitution with a portion of normal cells (46,XX) and a portion of X-monosomic cells (45,X). Due to the presence of a normal cell line, individuals with mosaicism usually tend to have milder clinical phenotypes, or clinical manifestations compared to individuals having only classic abnormal cell lines, i.e., whole trisomic Down syndrome patients. Variations in clinical phenotypes in mosaicism depend on the relative distribution of normal/abnormal cells in different tissues and organs, as well as on the physiological importance of affected organs in mediating body functions [6].

Mosaicism might be **somatic**, occurring in somatic cells, or **germinal** occurring in germline cells, i.e. sperms and ova. Also,

it might be chromosomal mosaicism, with a cell line having an extra chromosome, or single gene mosaicism when one of the cell lines having a mutant gene present in all cells of this abnormal cell line. Typically, somatic mosaicism is not passed to future generations. However, somatic mosaicism with a population of cells having a mutant gene can cause pathological consequences like carcinogenesis. If a mutation happens in germline mosaicism, a population of germ cells having the mutation might result leading to the transmission of the disorder to future generations. Germline or gonadal mosaicism for mutations of genes causing autosomal dominant or X-linked disorders often accounts for unexpected occurrence and recurrence of the disorder in offspring of phenotypically normal parents. Genetic disorders known to be caused by this abnormal inheritance mechanism, in addition to the classic Mendelian pattern of inheritance, include Duchenne muscular dystrophy, osteogenesis imperfecta (brittle bone disease) and neurofibromatosis type I. germinal mosaicism has to be considered in families with many affected offspring with well-defined single gene molecular or cytogenetic defects which cannot be revealed in either of their parents.

7. Chromosomal aberrations

Chromosomal abnormalities comprise many different types which can involve a whole chromosome or just a segment of a chromosome. In either situation, the abnormalities may affect chromosome numbers, **numerical** chromosomal aberrations, or chromosome structure, **structural** chromosomal abnormalities. Numerical whole chromosomal aberrations include X-monosomy (45,X)/X-trisomy (47,XXX)/X-tetrasomy (48,XXXX) and many different autosomal trisomies, e.g. 13, 18 and 21 trisomy. Multiple numerical abnormalities of chromosomes include exceptional cases of **hypodiploidy** and **hyperdiploidy** seen only in malignant cells. Abnormalities of the whole haploid set of chromosomes can lead to rare cytogenetic defects like triploidy (69 chromosomes) and tetraploidy (92 chromosomes). **Endoreduplication** refers to the situation where replication of DNA leading to the duplication of chromosome number happens without concomitant cell division thus resulting in a cell with two diploid (92) genomes. This condition is occasionally observed in rapidly growing and dividing cells, like hepatocytes and bone marrow cells. Structural chromosomal aberrations comprise a wide spectrum of abnormalities including translocations, inversions, deletions, duplications, ring chromosome formation, isochromosome formation, chromosome breakage and many others [7].

Most instances of chromosomal abnormalities happen as random events during the formation of reproductive cells or in early fetal development. Obviously, chromosomal disorders do not conform with Mendelian patterns of inheritance. However, recurrence of a structural chromosomal anomaly in offspring of a parent who carries a constitutional chromosomal aberration might happen. Due to the recombination of chromosomal segments during gametogenesis, different gametes of a person carrying a constitutional structural abnormality might get the defective segments albeit with different genetic constitutions of each. Occurrence of offspring with varying clinical phenotypes suggestive of a chromosomal disorder in a family with phenotypically normal parents should raise the suspicion of carrying a chromosomal rearrangement which can be detected by cytogenetic diagnostic techniques. Prenatal cytogenetic studies of all future pregnancies should be performed in these situations.

8. Microdeletion/microduplication/microtriplication defects

These tiny peculiar defects represent submicroscopic structural chromosomal abnormalities that cannot be detected by ordinary cytogenetic investigation, rather they are amenable to diagnosis by molecular cytogenetic techniques like Fluorescence in situ hybridization (FISH). In view of the large numbers of genes distributed and located on functional regions of the chromosomes, even tiny defects of chromosomes like microdeletion/microduplication/microtriplication can involve considerably large numbers of gene in affected segments. Because of concomitant participation of many contiguous genes of these segments in formulating the clinical phenotypes caused by these defects, contiguous gene disorders with variable, sometimes, wide spectrum of clinical manifestations are observed. For example, some patients with Cri-du-Chat, or cat cry, syndrome may have the deletion of the entire micro segment on the short arm of chromosome 5 (5p). However, the essential region underlying the pathognomonic clinical phenotype of the disorder involves genes located in the critical region 5p15.2. The high pitched cry gene maps to 5p15.3 while genes accounting for the remaining features map to a small region of 5p15.2. It is estimated that about 100 genes reside in this region. Deletions that do not include these critical genes located in 5p15.2/15.3 present varying clinical phenotypes ranging from microcephaly, facial dysmorphism, severe mental retardation and multiple congenital anomalies to essentially clinically normal phenotype.

Because of the common occurrence of microdeletion/microduplication/microtriplication regions along many chromosomes and at the telomeres, the number of disease phenotypes attributed to this abnormal pathogenetic mechanism is steadily increasing. Examples of these diseases include the William syndrome, DiGeorge syndrome, velocardiofacial anomaly, Shprintzen syndrome, Miller–Dieker lissencephaly syndrome, Wolf–Hirschhorn syndrome, Cri du Chat syndrome, Smith–Magenis syndrome, Langer–Giedion syndrome, Saethre–Chotzen syndrome and retinoblastoma. Also, cases of many diseases caused by different pathogenetic mechanisms, e.g., the Prader–Willi/Angelman syndromes and the Beckwith–Wiedemann syndrome caused by defective imprinting/uniparental disomy, are also caused by this peculiar cytogenetic defect.

9. Polygenic defects

Polygenic defects refer to genetic disorders caused by the combined effects of many mutant genes. This pathogenetic mechanism underlies the development of a considerable number of congenital malformations because normal differentiation, development and growth of embryonic and fetal tissues and organs require the additive functions of large numbers of genes. Polygenic defects are postulated to represent the commonest genetic component in multifactorial diseases. Examples of multifactorial diseases with a polygenic genetic background include complex congenital malformations of the heart and the nervous system, non-insulin dependent type of diabetes mellitus,

obesity, allergic and autoimmune disorders, hypertension, inflammatory bowel disease and intellectual disability [8]. Cancer represents a drastic example of genetic disorders caused by disturbed polygenic effects of many tumor-promoting and tumor suppressor genes. The polygenic background in carcinogenesis might be purely genetic or it might represent the genetic component in tumors caused by multifactorial pathogenetic mechanisms. The environmental effectors in these pathogenetic mechanisms include **carcinogens** that selectively promote functional overexpression of proto-oncogenes with or without concomitant suppression of tumor suppressor genes, **clastogens** that induce chromosome breaks and instability leading to disruption of the structural integrity of tumor suppressor genes or to chromosomal translocations/rearrangements leading to overexpression of proto-oncogenes and non-specific mutagens capable of inducing similar defects.

Conflict of interest

The author declares no conflict of interest.

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