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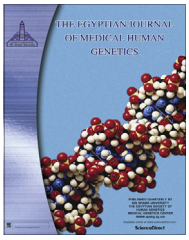

EDUCATIONAL CORNER OF THE ISSUE

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]