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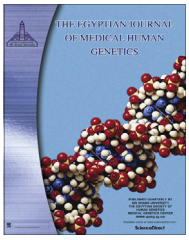

REVIEW

Biological imprinting: Some genetic considerations

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microRNA;
Chromatin modifications;
Pyknons

Abstract Genetic imprinting represents one of the most puzzling, still unexplained, phenomena in genetics. Changing some agreed upon concepts and redefinition of some common traditional terms in classical genetics seems imperative for understanding the nature of imprinting, as well as for interpretation of possible mechanisms implicated in its occurrence.

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1. Introduction

Genomic imprinting refers to differential expression of chromosomes, parts of chromosomes, single genes or sets of genes dependent on which of the two sexes they are inherited from, i.e., their parental origin. Following the establishment of imprinting in the male and female germ lines, respectively, the two parental genomes exhibit functional differences at fertilization [1]. Some sex differences in expression of inherited traits may result from genetic imprinting. To achieve imprinting, some genetic materials can be modified during gamete production or early embryonic development in one of the two sexes, so the traits determined by the imprinted genes are expressed differently than would be expected under typical Mendelian inheritance. A growing body of evidence points to methylation of cytosine residues in the context of cytosine–guanine (CpG) dinucleotides as the mechanism of imprinting. Such methylation, especially if it occurs in the promoter regions of genes, can nullify the ability of the genes to be transcribed. Certain genes that can be imprinted will be methylated in the production of sperm, others in the production of ova, and they can be reactivated by demethylation when they pass through gametogenesis in the opposite sex. It is still not known why certain alleles are subject to imprinting while others are not, and why they are more likely to be imprinted in one sex than the other.

Amplification of genes with functional overexpression, rather than inactivation or silencing, might result as a consequence of imprinting, that is, as the gene passes through gametogenesis in one of the sexes, sections of it become duplicated and the gene thereby gets amplified and shows abnormal copy number increase. This is seen in neuroblastoma, where an increased number of DNA segments containing the paternal N-myc protooncogene are detected. A similar phenomenon occurs in Huntington's chorea where amplification of segments of DNA in the gene is limited, exclusively, to the paternal HC genes inherited from the fathers.

Though genomic imprinting, which results in parental-specific silencing or suppression of gene expression especially during early development, is proposed to be the major mechanism that prevents occurrence of parthenogenesis in mammals, it can, also, result in development of many genetic diseases if detrimental mutations affect the other active expressing allele. Genetic diseases resulting from this particular pathogenetic mechanism are referred to as imprinting disorders and include many diseases like Beckwith–Wiedemann syndrome, Silver–Russell syndrome, Prader–Willi syndrome and Angelman syndrome [2].

2. Genetic mutations

The classic definition of genetic **mutation** entails any structural change in the genetic material at any of its organizational levels, nucleotide/gene/chromosome/whole genome, leading in most instances to deleterious functional alterations. At the single nucleotide level, mutational changes, referred to as point mutations, comprise structural changes of the nucleotides, or bases, of the gene by deletion/addition/replacement leading to pathogenetic defects that include **frame shifting** (change of the base sequence due to addition or deletion of one or two bases with consequent shifting of the codon-frame of the gene and the amino acid frame of the defined protein), **missense** alteration (change of the amino acid defined by the original code comprising the original base to another different amino acid defined by the new code comprising the new base), **same-sense** alteration (change of a base of a codon to another base forming a new codon that defines the same amino acid due to degeneracy of the genetic code) and **non-sense** alteration (change of one base of a functional codon that specifies a particular amino acid to another base leading to the formation of a stop or termination codon that does not code for, or define, any amino acid). Change of a stop codon to a functioning codon leading to aberrant continuation of translation and synthesis of longer polypeptide chains will be referred to, arbitrarily, as **re-sense mutation**, an abbreviation of regaining sense, mutation.

3. Epigenetic alterations

The corresponding classic definition of **epigenetic** changes entails structural changes of the bases, affecting neither their number nor their sequence along the affected region, that can alter gene expression. For example, methylation of cytosine bases along the gene promoter will not change the number of methylated bases or their sequence along the epigenetically altered region but can alter their expression. Methylation of bases is a reversible mutational change mediated by specific enzymes that required S-adenosyl-methionine as methyl donor, methyltransferases, and reversed by specific demethylases. Similarly, methylation of specific regions of the DNA-associated proteins, primarily histones, is mandatory for maintaining vital functional aspects of the genome. For instance, maintaining a proper balance of histone methylation, by the opposing activities of lysine methyltransferases and lysine demethylases, is critical for genomic stability, cell cycle progression, gene regulation, DNA replication, and cancer prevention [3]. Modulations of gene expression induced by epigenetic changes of the gene, e.g., by methylation, and/or epigenetic alterations causing structural modifications of gene-associated proteins, e.g., by methylation/acetylation/phosphorylation/, can be attributed to many causes including, for instance, promotion of heterochromatin formation [4], changes of protein function and protein–protein interactions [5].

Epigenetic changes, irrespective of their nature, are better considered as a specific subcategory of genetic mutations, since structural alterations induced by these changes, e.g., DNA-methylation/histone modifications, can result in functional disturbances, like suppression of transcription. Postulations, based on hypothetical mechanisms as well as on some

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