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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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Basic Concepts In Medical Genetics

JE Gale



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Table of Contents Basic Concepts In Medical Genetics

1. Understanding the eBook Basic Concepts In Medical Genetics
 - The Rise of Digital Reading Basic Concepts In Medical Genetics
 - Advantages of eBooks Over Traditional Books
2. Identifying Basic Concepts In Medical Genetics
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Basic Concepts In Medical Genetics
 - User-Friendly Interface
4. Exploring eBook Recommendations from Basic Concepts In Medical Genetics
 - Personalized Recommendations
 - Basic Concepts In Medical Genetics User Reviews and Ratings
 - Basic Concepts In Medical Genetics and Bestseller Lists
5. Accessing Basic Concepts In Medical Genetics Free and Paid eBooks
 - Basic Concepts In Medical Genetics Public Domain eBooks
 - Basic Concepts In Medical Genetics eBook Subscription Services
 - Basic Concepts In Medical Genetics Budget-Friendly Options
6. Navigating Basic Concepts In Medical Genetics eBook Formats
 - ePub, PDF, MOBI, and More
 - Basic Concepts In Medical Genetics Compatibility with Devices
 - Basic Concepts In Medical Genetics Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Basic Concepts In Medical Genetics
 - Highlighting and Note-Taking Basic Concepts In Medical Genetics
 - Interactive Elements Basic Concepts In Medical Genetics
8. Staying Engaged with Basic Concepts In Medical Genetics

- Joining Online Reading Communities
- Participating in Virtual Book Clubs
- Following Authors and Publishers Basic Concepts In Medical Genetics
- 9. Balancing eBooks and Physical Books Basic Concepts In Medical Genetics
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Basic Concepts In Medical Genetics
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Basic Concepts In Medical Genetics
 - Setting Reading Goals Basic Concepts In Medical Genetics
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Basic Concepts In Medical Genetics
 - Fact-Checking eBook Content of Basic Concepts In Medical Genetics
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
- 14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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