WHEN THEY MUTATE

Genetic Disorders & Their Manifestations

Dr. Apurva Mishra
Prof. R.K. Pandey

OnlineGatha – The Endless Tale

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MESSAGE

Learning is a continuous process with unlimited and unexpected boundaries in field of academics. Medical diagnostics is a fast changing field of medical science evolving concepts and techniques. Advances in genetic analysis especially DNA sequencing and genetic engineering technologies have allowed us to look deeply in diversity of life. I congratulate authors for their efforts to compile book on genetic syndromes and their manifestations, including advanced diagnostic techniques.
The book will be popular among students wordwide

Best wishes

Ravi Kant

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FOREWARD

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I am glad to write a Foreward for "When they mutate, Genetic disorders & their Manifestations" authored by Prof. R. K. Pandey, Professor and Head, Department of Paediatric and Preventive Dentistry, King George's Medical University, Lucknow.

Dental management of the children with special needs is a challenging yet rewarding experience. Clinicians who manage and treat these special children require a thorough understanding of the nature and effects of various disabilities experienced by these children.

This comprehensive textbook, *e*xplains in great detail the medical and dental aspects of the various disabilities and

conditions seen in children with genetic disorders and its manifestations. The topics included in this book cover the length and breadth of literature available in this field at the time of publication and is collated in a format which is easy to read and understand. I would like to congratulate the author for writing such a great textbook. I am confident that this book will be an excellent source of information and handy reference tool for students and clinicians who treat children with special needs. I wish him good success in all his endeavours.

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PREFACE

To know, is to know that you know nothing.

That is the meaning of true knowledge.

Socrates

To accomplish an academic pursuit it requires a conscious effort, to acquire the knowledge, to practice, preach and finally to document what is practiced and preached. The first edition of this book is designed for comprehensive learning and understanding about genetic disorders for the undergraduate and post graduate medical students. It lays emphasis on mutation, types on mutations and clinical manifestations of each genetic disorder. We also tried to enlist few major advanced diagnostic techniques for genetic disorders, with detailed procedure which will provide a deep insight and will enhance the learning of molecular genetic techniques.

We hope students and faculties will find this book useful. We would be happy to receive feedback for improvement in subsequent edition.

Dr. Apurva Mishra
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INTRODUCTION:

Genetic disorders are still perceived as an uncommon event in our general population. However the literature reveals that every year an estimated 7.9 million children (6 percent of total births worldwide) are born with a serious birth defect of genetic or partially genetic origin. Additional hundreds of thousands more are born with serious birth defects of post-conception origin, including maternal exposure to environmental agents (teratogens) such as alcohol, rubella, syphilis and iodine deficiency that can harm a developing fetus.

The expression of various human traits depends on interaction between genes and environment i.e. genetic vs nongenetic (infections, teratogens) factors. Disorders caused due to mutation in a single gene can be due to influence of the environmental factors eg. cystic fibrosis and sickle cell disorder. Similarly infection with HIV-1 can led to genetic polymorphism.

As per data presented by Global Report on Birth Defects (New York) in 2006, birth defects are a global problem, but their impact is particularly severe in middle- and low income countries where more than 94 percent of the births with serious birth defects and 95 percent of the deaths of these children occur. The proportion of births with birth defects as well as the absolute number of births are much higher in middle and low-income countries than in high-income countries because of sharp differences in maternal health and other significant risk factors, including poverty, a high percentage of older mothers, a greater frequency of consanguineous marriages and the survival advantage against malaria for carriers of sickle cell, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency genes. According to the data in this report, five common serious birth defects of genetic or partially genetic origin in 2001 were: (1) congenital heart defects ; (2) neural tube defects (3) the hemoglobin disorders (thalassemia, and sickle cell disease) (4) Down syndrome

(trisomy 21) and (5) glucose-6-phosphate dehydrogenase (G6PD) deficiency. Combined, these five conditions account for about 25 percent of all of birth defects of genetic or partially genetic origin.

GENETIC TERMINOLOGIES:

ALLELES: Alternative forms of a gene found on the same locus on homologous chromosomes in an individual. The term coined by Bateson and Saunders (1902) for characters which are alternative to one another in Mendelian inheritance (Gk. Allelon, one another; morphe, form). Now the term allele is used for two or more alternative forms of a gene resulting in different gene products and thus different phenotypes. In a haploid set of chromosomes there is only one allele at its specific locus. Diploid organisms have 2 alleles at a given locus, i.e. a normal and a mutant allele. A single allele for each gene locus is inherited separately from each parent (e.g., at a locus for eye colour the allele might result in blue or brown eyes). An organism is homozygous for a gene if the alleles are identical, and heterozygous if they are different.

ALLELIC HETEROGENECITY: The causation of a diseased phenotype by variety of different genotype at same locus.

BASE PAIR: Two nitrogenous (purine or pyrimidine) bases (adenine and thymine or guanine and cytosine) held together by weak hydrogen bonds. Two strands of DNA are held together in the shape of a double helix by the bonds between base pairs. The number of base pairs is often used as a measure of length of a DNA segment, eg 500 bp.

CHROMOSOME JUMPING: A technique of isolating clones from a genomic library that are not contiguous by skipping a region between known points on the chromosome. Done

usually to bypass regions that are difficult or impossible to walk through or regions known not to be of interest.

CHROMOSOMES: The term was proposed by Waldeyer (1888) for the individual threads within a cell nucleus (gk. chroma, colour; soma, body). The self-replicating genetic structures of cells containing the cellular DNA that bears in its nucleotide sequence the linear array of genes. In prokaryotes, chromosomal DNA is circular, and the entire genome is carried on one chromosome. Eukaryotic genomes consist of a number of chromosomes whose DNA is associated with different kinds of proteins. They are collection of genes or the carrier of genetic codes. Human beings have 23 pairs of chromosomes (46) out of which 22 pairs are autosomes and a pair of sex chromosomes.

CODON: **T**he term proposed by Crick (1963) for the sequence of nucleotides in DNA or RNA.which is responsible for determining that a specific amino acid shall be inserted into a polypeptide chain. There is more than one codon for most amino acids. It has now been established that the codon is a triplet of nitrogenous bases in DNA or RNA that specifies a single amino acid.

CONGENTIAL: Conditions present at birth.

DOMINANT: The term which Mendel (1866) introduced for a character which is manifest in all the members of the first filial generation (F1) from a cross between two pure-breeding, homozygous strains differing in respect of this character, and which is evident in three quarters of the individuals of the second filial (F2) generation.

FAMILIAL CONDITIONS: Conditions that appears to cluster with in families (genetic or non-genetic).

GENE EXPRESSION: The process by which a gene's coded information is converted into the structures present and operating in the cell. Expressed genes include those that are transcribed into mRNA and then translated into protein and those that are transcribed into RNA but not translated into protein (e.g., transfer and ribosomal RNAs). The degree of expression is called expressivity.

GENE MAPPING: Determination of the relative positions of genes on a DNA molecule (chromosome or plasmid) and of the distance, in linkage units or physical units, between them.

GENE POOL: All of the alleles available among the reproductive members of a population from which gametes can be drawn.

GENE: A segment of DNA which codes for the synthesis of a polypeptide. Gene is the basic unit of hereditary. The term coined by Johannsen (1909) for the fundamental physical and functional unit of heredity. The word gene was derived from De Vries' term pangen, itself a derivative of the word pangenesis which Darwin (1868) had coined. A gene is an ordered sequence of nucleotides located in a particular position (locus) on a particular chromosome that encodes a specific functional product (the gene product, i.e. a protein or RNA molecule). It includes regions involved in regulation of expression and regions that code for a specific functional product.

GENETIC CODE: The sequence of nucleotides, coded in triplets (codons) along the mRNA, that determines the sequence of amino acids in protein synthesis. The DNA sequence of a gene can be used to predict the mRNA sequence, and the genetic code can in turn be used to predict the amino acid sequence.

GENETIC DRIFT: The random change of the occurance of a particular gene in a population; genetic drift is thought to be one cause of speciation when a group of organisms is separated from its parent population. Ramdom genetic drift: Changes in allelic frequency due to sampling error. Changes in allele frequency that result because the genes appearing in progenies are not a perfectly representative sampling of the parental genes. (eg. in small populations)

GENOTYPE: The term proposed by Johannsen (1909) for the hereditary constitution of an individual, or of particular nuclei within its cells.

HEREDITARY: Conditions that can be transmitted from parents to off-springs.

HOMOLOGUS CHROMOSOMES: A pair of chromosomes containing the same linear gene sequences, each derived from one parent. Humans normally have 22 pairs of homologous chromosomes and 2X chromosomes (female) or 1X and 1Y chromosome (male).

KARYOTYPES: A photomicrograph of an individual's chromosomes arranged in a standard format showing the number, size, and shape of each chromosome type; used in low-resolution physical mapping to correlate gross chromosomal abnormalities with the characteristics of specific diseases.

LOCUS: The position of a gene on a chromosome or other chromosome markers; also, the DNA at that position. The use of the term locus is sometimes restricted to main regions of DNA that are expressed.

MENDEL'S FIRST LAW: The two members of a gene pair segregate from each other during meiosis; each gamete has an equal probability of obtaining either member of the gene pair.

MENDEL'S SECOND LAW: The law of independent assortment; unlinked or distantly linked segregating gene pairs assort independently at meiosis.

MOSAICISM: Condition in which an individual harbors 2 or more genetically distinct cell lines; results from a genetic change after formation of a zygote, ie postzygotic event.

MUTATION: A change in the DNA of a particular gene. The term which De Vries introduced into biological literature for an abrupt change of genotype which is inherited. Any permanent and heritable change in DNA sequence. Types of mutations include point mutations, deletions, insertions, and changes in number and structure of chromosomes.

NUCLEOTIDE: A subunit of DNA or RNA consisting of a nitrogenous base (purine in adenine and guanine, pyrimidine in thymine, or cytosine for DNA and uracil cytosine for RNA), a phosphate molecule, and a sugar molecule (deoxyribose in DNA and ribose in RNA). Depending on the sugar the nucleotides are called deoxyribonucleotides or ribonucleotides. Thousands of nucleotides are linked to form a DNA or RNA molecule.

PEDIGREE: A diagram mapping the genetic history of a particular individual or family.

PENETRANCE: Probability of an individual with diseased genotype to exhibit diseases. Term coined by Voigt (1926) for the percentage with which a dominant or homozygous recessive gene expresses itself in the phenotype. Quantitative concept of gene expression. It depends both on genotype and environment. If all individuals of the genotype show the trait, penetrance is 100%.

PHENOTYPE: The physical or clinical appearance of an individual determined by a pair of genes at a given locus or genotype. The phenotypic expression may vary as per modifying factors (genetic or non-genetic).

PLASMID: **A**utonomously replicating, extrachromosomal circular DNA molecules, distinct from the normal bacterial genome and nonessential for cell survival under nonselective conditions. Some plasmids are capable of integrating into the host genome and are used as a cloning vector for small pieces of DNA (typically 50 to 5000 base pairs) by insertion into the plasmid. A number of artificially constructed plasmids are used as cloning vectors.

PLEIOTROPHIC GENES: Genes that have more than one discernible effect on phenotype. For eg. Marfan's syndrome characterized by ocular, cardiovascular and skeletal disorders.

POLYGENIC DISORDERS: Genetic disorders resulting from the combined action of alleles of more than one gene (e.g., heart disease, diabetes, and some cancers). Although such disorders are inherited, they depend on the simultaneous pressence of several alleles; thus the hereditary patterns are usually more complex than those of single-gene disorders.

PROBABILITY: The expectation of the occurrence of a particular event. Likelihood of the occurrence of any event in the doctrine of chances, or the ratio of the number of favorable chances to the whole number of chances, favourable and unfavourable.

PROTEONOMICS: Systematic analysis of protein expression of normal and diseased tissues that involves the separation, identification and characterization of all of the proteins in an organism.

RECESSIVE: Mendel (1866) proposed this tterm for a character which was not evident in the first filial generation (F1) of a cross between two pure-breeding strains differing in respect of this character, and which re-appeared in one quarter of the second

filial generation (F2). The recessive character is expressed phenotypically in the homozygous or hemizygous state.

SINGLE GENE DISORDER: Hereditary disorder caused by a mutant allele of a single gene (e.g., Duchenne muscular dystrophy, retinoblastoma, sickle cell disease in human beings).

TRAIT: An attribute or character of an individual within a species for which heritable differences can be defined.

TRANSCRIPTION: The synthesis of an RNA copy from a sequence of DNA (a gene); the first step in gene expression.

TRANSFORMATION: A process by which the genetic material carried by an individual cell is altered by incorporation of exogenous DNA into its genome. The phenomenon was first described by Griffith (1928) in Diplococcus pneumoniae.

TRANSGENIC: Containing foreign DNA eg. transgenic mice contain foreign (eg. human) DNA sequences in addition to the complete mouse genome.

TRANSLOCATION: Transfer of a segment of a chromosome to a non-homologous chromosome. Translocations are usually reciprocal.

VARIABLE EXPRESSIVITY: Two individual with same genotype and different phenotype. The reasons behind variation in expression can be due to influence of modify factors which may be either be environmental or due to influence of other genes.