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Inborn errors of metabolism

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CHROMOSOME ABNORMALITIES

- **Chromosome disorders form a major category of genetic disease (congenital malformations and mental retardation).**
- **Chromosome disorders play an important role in the pathogenesis of malignant disease.**
- **Abnormalities of chromosomes may be either numerical or structural and may involve one or more autosomes, sex chromosomes, or both.**

- **The most common type of clinically significant chromosome abnormality is aneuploidy, an abnormal chromosome number due to an extra or missing chromosome**
- **Reciprocal translocations (an exchange of segments between non-homologous chromosomes).**

Abnormalities of Chromosome Structure

- **Structural rearrangements result from chromosome breakage, followed by reconstitution in an abnormal combination.**
- **Structural rearrangements are defined as balanced, if the chromosome set has the normal complement of chromosomal material, or unbalanced, if there is additional or missing material.**

Genomic Imprinting

- **The expression of the disease phenotype depends on whether the mutant allele or abnormal chromosome has been inherited from the father or from the mother.**
- **Differences in gene expression between the allele inherited from the mother and the allele inherited from the father are the result of genomic imprinting.**

- **Imprinting is a normal process caused by alterations in chromatin that occur in the germline of one parent, but not the other, at characteristic locations in the genome. These alterations include the covalent modification of DNA, such as methylation of cytosine to form 5-methylcytosine, or the modification or substitution in chromatin of specific histone types which can influence gene expression within a chromosomal region.**

- **Imprinting affects the expression of a gene but not its primary DNA sequence. It is a reversible form of gene inactivation but not a mutation, and thus it is an example of what is called an *epigenetic* effect.**
- **Epigenetics is an area of increasing importance in human and medical genetics, with significant influences on gene expression and phenotype, both in normal individuals and in a variety of disorders, including cytogenetic abnormalities.**

Single-gene disorders

- **Single-gene traits caused by mutations in genes in the nuclear genome are often called mendelian because, like the characteristics of garden peas studied by Gregor Mendel.**
- **Mutations in genes result in recessive, dominant, X-linked, and mitochondrial inheritance patterns. Variation in genes**

- **For many genes, there is a single prevailing allele, present in the majority of individuals, that geneticists call the wild-type or common allele.**
- **The other versions of the gene are variant or mutant alleles that differ from the wild-type allele because of the presence of a mutation, a permanent change in the nucleotide sequence or arrangement of DNA.**
- **A given set of alleles at a locus or cluster of loci on a chromosome is referred to as a haplotype.**

- **Variant alleles arose by mutation at some time. If there are at least two relatively common alleles at the locus in the population, the locus is said to exhibit polymorphism.**
- **Loci may also have one or more rare, variant alleles. Some of these rare alleles were originally identified because they cause genetic disease; others may increase susceptibility to disease, and yet others are of no known significance to health.**

- **The term mutation is used in medical genetics in two senses: sometimes to indicate a new genetic change that has not been previously known in a family, and sometimes merely to indicate a disease-causing mutant allele.**

Genotype and Phenotype

- **The genotype of a person is the set of alleles that make up his or her genetic constitution, either collectively at all loci or, more typically, at a single locus.**
- **The phenotype is the observable expression of a genotype as a morphological, clinical, cellular, or biochemical trait.**

- **A single-gene disorder is one that is determined primarily by the alleles at a single locus. When a person has a pair of identical alleles at a locus encoded in nuclear DNA, he or she is said to be homozygous (a homozygote); when the alleles are different, he or she is heterozygous (a heterozygote or carrier).**

- **The term compound heterozygote is used to describe a genotype in which two different mutant alleles of the same gene are present, rather than one normal and one mutant. In the special case in which a male has an abnormal allele for a gene located on the X chromosome and there is no other copy of the gene, he is neither homozygous nor heterozygous and is referred to as hemizygous.**

Dominant and Recessive Inheritance

Recessive Inheritance:

- **A phenotype expressed only in homozygotes (or, for X-linked traits, male hemizygotes) and not in heterozygotes is recessive.**
- **Most of the recessive disorders described to date are due to mutations that reduce or eliminate the function of the gene product, so-called loss-of-function mutations.**

Dominant Inheritance

- **A phenotype expressed in both homozygotes and heterozygotes for a mutant allele is inherited as a dominant.**
- **Dominant disorders occur whether or not there is normal gene product made from the remaining normal allele. In a pure dominant disease, homozygotes and heterozygotes for the mutant allele are both affected equally.**

- **On occasion, phenotypic expression of two different alleles for a locus occurs, in which case the two alleles are termed codominant. One well-known example of codominant expression is the ABO blood group system.**
- **Most commonly, dominant disorders are more severe in homozygotes than in heterozygotes, in which case the disease is called incompletely dominant (or semidominant).**

Mitochondrial Inheritance

The Mitochondrial Genome

- **A small and important fraction of proteins is encoded by genes within the mitochondrial genome.**
- **Mitochondrial genome consists of a circular chromosome, 16.5 kb in size, that is located inside the mitochondrial organelle, not in the nucleus.**
- **Most cells contain at least 1000 mtDNA molecules, distributed among hundreds of individual mitochondria.**