# Chapter 7

# Genetic and Congenital Disorders



## Terminology of Genetic and Congenital Disorders

- Congenital
- Allele
- Gene locus
- Gene mutation
- Genotype
- Phenotype
- Homozygous
- Heterozygous
- Polymorphism
- Gene penetrance
- Gene expression

## Causes of Birth Defects

- **Genetic Factors**
  - Single-gene or multifactorial inheritance or chromosomal aberrations
- **Environmental Factors** (Fetal Development)
  - Maternal disease, infections, or drugs taken during pregnancy
- **Intrauterine Factors** (Rare)
  - Fetal crowding, positioning, or entanglement of fetal parts with the amnion



## Question

- Which of the following causes of gene mutation is least common?
  - A. Genetic factors
  - B. Environmental factors
  - C. Intrauterine factors

## Answer

- C. Intrauterine factors
- Rationale: Due to the need for multiple births or abnormal development.



## Characteristics of Single-Gene Disorders

- Caused by a single defective or mutant gene
  - May be present on an autosome or the X chromosome
  - May affect one member or both members of an autosomal gene pair
- Defects follow the mendelian patterns of inheritance
- Characterized by their patterns of transmission
  - Obtained through a family genetic history

## Result of Single-Gene Disorders

- Formation of an abnormal protein or decreased production of a gene product
- Defective or decreased amounts of an enzyme
- Defects in receptor proteins and their function
- Alterations in nonenzyme proteins
- Mutations resulting in unusual reactions to drugs



## Disorders of Single-Gene Inheritance (Mendelian)

- **Autosomal Dominant**
  - A single mutant allele from an affected parent is transmitted to an offspring regardless of sex.
- **Autosomal Recessive**
  - Manifested only when both members of the gene pair are affected (both parents unaffected, but carriers)
- **X-linked Recessive**
  - Always associated with the X chromosome; the inheritance pattern is predominately recessive.

## Autosomal Dominant Disorders

- **Marfan Syndrome**
  - A connective tissue disorder manifested by changes in the skeleton, eyes, and cardiovascular system
- **Neurofibromatosis (NF)**
  - A condition involving neurogenic tumors that arise from Schwann cells and other elements of the peripheral nervous system



## Autosomal Recessive Disorders

- **Phenylketonuria (PKU)**
  - A rare metabolic disorder caused by a deficiency of the liver enzyme phenylalanine hydroxylase
- **Tay-Sachs Disease**
  - A variant of a class of lysosomal storage diseases, known as gangliosidoses
  - Gangliosides in the membranes of nervous tissue are deposited in neurons of the central nervous system and retina because of a failure of lysosomal degradation

## X-Linked Disorder

- Fragile X syndrome
  - Associated with a fragile site on the X chromosome where the chromatin fails to condense during mitosis
  - Affects more males than females
    - Approximately 1 in 1000 male infants
  - Second most common cause of mental retardation after Down syndrome



## Characteristics of Multifactorial Inheritance Disorders

- Caused by multiple genes and environmental factors.
  - The exact number of genes is not known.
- Traits do not follow a clear-cut pattern of inheritance.
  - Disorders can be expressed during fetal life and be present at birth, or expressed later in life.

## Examples of Multifactorial Inheritance Disorders

- Cleft lip or palate
- Clubfoot
- Congenital dislocation of the hip
- Congenital heart disease
- Pyloric stenosis
- Urinary tract malformation



## Question

- Is the following statement true or false?

- Multifactorial disorders are simply single-gene mutations and the results of the environmental interactions with that mutation.

## Answer

- False
- Rationale: By definition, multifactorial diseases involve multiple interactions between the environment and genes (single and multiple genes).



## Results of Chromosomal Disorders

- Reproductive wastage (early gestational abortions)
- Congenital malformations
- Mental retardation
- Linked to more than 60 identifiable syndromes present in birth

## Types of Chromosomal Disorders

- Alterations in chromosome duplication
- Alterations in chromosome number
  - Trisomy 21 (Down syndrome)
  - Monosomy X (Turner syndrome)
  - Polosomy X (Klinefelter syndrome)
- Alterations in chromosome structure



## Mitochondrial DNA Disorders

- Subject to mutations at a higher rate than nuclear DNA
  - No repair mechanisms
- Disorders of mitochondrial genes interfere with production of cellular energy.
- Lead to the production of energy reactive oxygen species, or disrupt the generation of signals that initiate apoptosis
- Commonly associated with neuromuscular disorders

## Disorders Caused by Environmental Influences

- Teratogenic agents: produce abnormalities during embryonic or fetal development
- Most susceptible to these agents during organogenesis



## Teratogenic Agents

- Radiation
- Chemicals and drugs
  - Fetal alcohol syndrome
  - Cocaine babies
  - Folic acid deficiency
- Infectious agents

## Question

- Which of the following compounds can be considered to be teratogenic?
  - A. Radiation
  - B. Chemicals
  - C. Drugs
  - D. Infectious agents
  - E. All the above
  - F. None of the above



## Answer

- E. All of the above

- Rationale: Each of these agents can produce abnormalities during embryonic or fetal development.

## Criteria for Defining Fetal Alcohol Syndrome

- Prenatal or postnatal growth retardation
  - Weight or length below the 10th percentile
- Central nervous system involvement
  - Neurologic abnormalities
  - Developmental delays
  - Behavioral dysfunction
  - Intellectual impairment
  - Skull and brain malformation



## Criteria for Defining Fetal Alcohol Syndrome (cont.)

- A characteristic face
  - Short palpebral fissures (eye openings)
  - Thin upper lip
  - Elongated, flattened midface, and philtrum

## Effects of Cocaine Use During Pregnancy

- Decrease in uteroplacental blood flow
- Maternal hypertension
- Stimulation of uterine contractions
- Fetal vasoconstriction



## Other Medications During Pregnancy

- Possibilities of cytotoxic (cell-killing), antimetabolic, or growth-inhibiting activities
  - Vitamin A derivatives
  - Folic acid deficiency

## Infectious Agents During Pregnancy

- TORCH
  - Toxoplasmosis
  - Other
  - Rubella
  - Cytomegalovirus
  - Herpes
- Varicella-zoster virus infection
- Listeriosis
- Leptospirosis
- Epstein-Barr virus infection
- Tuberculosis and syphilis
- Human immunodeficiency virus (HIV)
- Human parvovirus (B19)



## Components of a Genetic Assessment

- Assessment of genetic risk and prognosis
- Detailed family history
- Pregnancy history
- Detailed accounts of birth process
- Accounts of postnatal health and development
- Physical examination of the affected child and family
- Laboratory tests

## Purposes of a Prenatal Diagnosis

- Provide parents with information needed to make informed choice about having a child with abnormality
- Provide reassurance and reduce anxiety among high-risk groups
- Allow parents at risk to begin pregnancy with assurance that knowledge about the presence or absence of a disorder can be confirmed with testing



## Methods Used for Fetal Diagnosis

- Maternal blood screening
- Ultrasonography
- Amniocentesis
- Chorionic villus sampling
- Percutaneous umbilical cord blood sampling
- Fetal biopsy
- Cytogenetic and biochemical analyses