1. Basic Human Pathology Lecture #3 Developmental and Genetic F...

Basic Human Pathology Lecture #3
Developmental and Genetic Factors in Disease

2007
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2. Introduction – Basic of Genetics

Introduction – Basic of Genetics

- Every cell in the human body, except RBCs, has DNA with the same genetic information
  - 23 pairs of chromosomes
  - Different types of cells express different genes to perform their functions
- Human genome - 46 chromosomes
  - 22 pairs of autosomes
  - One pair of sex chromosomes
    - XX in the female and XY in the male
- Genetic mistakes:
  - Chromosomal abnormalities
  - Genetic misspellings of the bases of the genetic code that composes a gene or allele

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3. Mendelian Genetics

Mendel discovered people may inherit defective genes from their parents
- If genetic mutation is dominant the gene must be inherited from only one parent to cause the disease
- If a disorder is recessive the defective gene must be inherited from both parents
- One who inherits a single recessive mutation can pass the defective gene on to his or her children
- Some diseases are linked to a gene defect on the X chromosome, meaning that the disease essentially as recessive inheritance in women and dominant inheritance in men

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4. Mendelian Genetics

Mendelian traits classification
- Autosomal dominant
  - Ex. – Huntington’s disease
- Autosomal recessive
  - Ex. – Tay-Sachs
- X-linked dominant
- X-linked recessive
- Y-linked disorders
- Mitochondrial disorders

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5. Genetic Predisposition to Disease

**Genetic Predisposition to Disease**

- Many health conditions linked to genetic mutations do **not** follow Mendel’s rules of inheritance
  - Specific mutations may predispose to periodontal disease, caries, diabetes, oral cancer, cardiovascular disease, and obesity
  - A genetic component has been identified in infectious diseases, cancer, and nearly every other type of human disease
- For many diseases, genetic mutations must interact with human behavior and environmental factors to result in disease

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6. Gene Defects

**Gene Defects**

- Alter cell function in several ways
- Different defects in the same gene can manifest in radically different ways
- Some genetic mutations force cells to produce malformed proteins that do not function properly; other mutations prohibit cells from producing proteins altogether
- Sometimes a genetic mutation produces a “defect” that is favorable to those that inherit them
  - Ex. - defective gene that protects against AIDS
    - Fails to produce the receptor on the immune cells’ surface so that HIV is unable to enter the cell and thus prevent replication of HIV and its dissemination

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7. Abnormal Fetal Development

Abnormal Fetal Development

- **Agenesis**
  - Complete absence of organ due to lack of development
  - Ex. - only one kidney

- **Dysgenesis**
  - Abnormal structure of an organ due to abnormal differentiation

- **Hypoplasia**
  - A small organ due to lack of development after normal differentiation
  - Ex. - short mandible (retrognathia); phocomelia

- **Aplasia**
  - A failure to develop an organ after differentiation has occurred

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8. Agenesis

Agenesis - Complete Absence of Both Kidneys
Adrenal Glands are Present

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9. Hypoplasia of Arm - Phocomelia

Hypoplasia of Arm - Phocomelia

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10. Developmental and Genetic Factors in Disease: Slide 10

Hypoplasia of Mandible and Cleft Palate – Pierre-Robin Syndrome

Retrognathic

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11. Developmental and Genetic Factors in Disease: Slide 11

Hypoplasia of Mandible – Treacher Collins Syndrome

Retrognathic

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12. Chromosomal Disorders

Chromosomal Disorders

- Changes in chromosome number or structure
  - Normal human cell (diploid) – 46 chromosomes = 22 pairs of autosomes and 2 sex chromosomes
    - Normal male = 46, XY
    - Normal female = 46, XX
  - Genetic mistakes - number of chromosomes is abnormal or parts (structure) of chromosomes broken or rearranged
    - Aneuploidy
    - Polyplody
    - Deletion
    - Inversion
    - Translocation
    - Isochromosome formation

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13. Chromosomal Disorders

Chromosomal Disorders

- **Aneuploidy**
  - Chromosome number that is not a multiple of 23, the normal haploid number
  - Most often caused by addition or loss of one or two chromosomes; result of
    - **Nondisjunction**
      - Failure of chromosomes to separate during meiosis or mitosis
    - **Anaphase lag**
      - Result in the *loss of a chromosome* during meiosis or mitosis
      - In early embryonic life can result in *mosaicism*
      - Individual develops two cell lines – one normal chromosome complement and the other with *monosity* (single residual chromosome)

14. Chromosomal Disorders

Chromosomal Disorders

- **Meiotic nondisjunction**
  - Lack of separation of chromosomal pairs in the first *meiotic* division of the gamete
  - Most common cause of aneuploidy
  - May result in aneuploid gametes (22 or 24 chromosomes = the loss or gain of a chromosome)
    - **Monosomy**
      - Loss of a chromosome with resultant abnormal zygote; the fetus usually dies
    - **Trisomy**
      - Gain of a chromosome
      - Ex. - Trisomy 21 - most common form is Down syndrome
    - **Sex chromosome**
      - Fetus survives with abnormal gonadal development
      - Ex. - Turner syndrome - XO
      - Ex. - Klinefelter’s syndrome - XXY
15. Chromosomal Disorders

Chromosomal Disorders

- Polyploidy
  - Chromosome number that is a multiple greater than two of the haploid number
    - Triploid - three times the haploid number
    - Tetraploid - four times the haploid number
  - Rarely compatible with life and usually results in spontaneous abortion

- Inversion
  - Reunion of a chromosome broken at two points, in which the internal fragment is reinserted in an inverted position
    - Paracentric and pericentric – same side vs. opposite side of the centromere, respectively

16. Chromosomal Disorders

Chromosomal Disorders

- Deletion
  - Most often absence of a portion of chromosome
    - Can be loss of entire chromosome
    - Denoted by the number of the chromosome, sex chromosomes, del (deletion), the sign for the chromosomal arm involved
      - 'p' for short arm (petite); 'q' for the long arm
        - Ex. - cri du chat syndrome
          - Partial loss of the short arm of chromosome #5
          - 46,XX,del(5p) females and 46,XY,del(5p) males
Chromosomal Disorders

Translocation

- Exchange of chromosomal segments between nonhomologous chromosomes
  - Denoted by a 't' followed by the involved chromosomes in numeric order
  - Ex. - translocation form of Down syndrome = t(14q;21q)

Translocation - (cont’d)

- Reciprocal or balanced translocation
  - Break in two chromosomes leading to an exchange of chromosomal material
  - No genetic material is loss so often clinically silent

- Robertsonian
  - Variant in which the long arms of two acrocentric chromosomes (short arms are very short) are joined with a common centromere and the short arms are lost
19. Chromosomal Disorders

**Chromosomal Disorders**

- **Isochromosome formation**
  - Result of transverse rather than longitudinal division of a chromosome -> two new chromosomes each with either two long arms or two short arms
  - Often the short arm chromosome is lost

- **Ring chromosome**
  - Circular reattachment with fragment of chromosome lost

20. Translocations

**Translocations**

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21. Robertsonian Translocation Consequence

Robertsonian Translocation Consequence

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22. Karyotype Analysis - Chromosomal Spreads

Karyotype Analysis - Chromosomal Spreads

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23. Nomenclature and Notation of Karyotype Analysis

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24. Sex Chromosomes: X inactivation and Barr body formation

Sex Chromosomes: X inactivation and Barr body formation

- X inactivation (exclusively in females)
  - Also called “Lyonization”
  - Process by which one X chromosome, of each pair in a cell, is randomly inactivated at an early stage of embryonic development
    - A large untranslated RNA molecule is associated with “coating” and inactivation of one of two X chromosomes
  - Normal females are mosaics with two distinct cell lines
    - Some cells have an active maternal X; others an active paternal X
25. Sex Chromosomes: X inactivation and Barr body formation

**Sex Chromosomes: X inactivation and Barr body formation**

- X inactivation - (cont’d)
  - Can be demonstrated if the female is heterozygous for an X-linked gene
  - Phenotypic differences between XO, XX, and multiple X genotypes thought to be caused by residual genes on the X chromosome that escape inactivation
- Extreme karyotype deviations in the sex chromosomes are compatible with life
  - Due to X inactivation (lyonization) and the relatively scanty genetic information carried by the Y chromosome

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26. Sex Chromosomes: X inactivation and Barr body formation

**Sex Chromosomes: X inactivation and Barr body formation**

- **Barr body (aka sex chromatin)**
  - Clumps of chromatin on the inner nuclear membrane in the interphase nuclei of all somatic cells in females
- **Lyon hypothesis**
  - Each Barr body represents one inactivated X chromosome
    - Normal females have one Barr body
    - Normal males have no Barr bodies
  - Ex. - XXXY cells have two Barr bodies
  - Therefore the number of Barr bodies is always one less than the number of X chromosomes

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27. Causes of Chromosomal Disorders

Causes of Chromosomal Disorders

- Idiopathic
  - Random
  - Most common
- Increasing maternal age
  - Ex. – trisomy 21 (Down syndrome)
    - Risk is 1 in 50 births over age 45
- Ionizing radiation
  - Can produce chromosomal abnormalities
- Drugs taken during pregnancy
  - Ex. - chemotherapy, aspirin, alcohol

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28. Chromosomal Disorders

Chromosomal Disorders

- Abnormalities of Autosomal Chromosomes
- Abnormalities of Sex Chromosomes
- Abnormalities Due to Increased Numbers of Trinucleotide Repeats
- Autosomal Dominant Disorders
- Autosomal Recessive Disorders
- X-linked Recessive Disorders
- X-linked Dominant Disorders
- Mitochondrial Mutations
- Non-classical Inheritance Patterns
- Fetal Abnormalities

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Abnormalities of Autosomal Chromosomes

- **Down syndrome (trisomy 21)**
  - Most frequently occurring chromosomal disorder
  - **Causes**
    - Trisomy 21
      - Accounts for 95% of cases; incidence increases with maternal age
      - Produced usually by maternal meiotic nondisjunction
    - Translocation
      - Accounts for 3%-5% of cases; no relation to maternal age
      - Caused by parental meiotic translocation between chromosome #21 and another chromosome
        - Fertilized ovum has three chromosomes bearing chromosome #21 material
      - Leads to a familial form with significant risk of the syndrome in subsequent children.

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Abnormalities of Autosomal Chromosomes

- Characteristics – Down syndrome
  - Marked by severe mental retardation
  - Phenotypic appearance
    - Large forehead, broad nasal bridge, wide-spaced eyes, epicanthal folds, large protruding tongue, small low-set ears
    - Brushfield spots
      - Small white spots on the periphery of the iris
    - Short, broad hands with curvature of the fifth finger, Simian crease, single palmar crease and unusually wide space between the first and second toes
  - Shortened life span
31. **Down syndrome - Features**

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32. **Abnormalities of Autosomal Chromosomes**

<table>
<thead>
<tr>
<th>Complications – Down syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>‒ Congenital heart disease</td>
</tr>
<tr>
<td>‒ Defects of the endocardial cushion including atrioventricular valve malformations and atrial and ventricular septal defects</td>
</tr>
<tr>
<td>‒ Acute leukemia (20-fold increase) esp. lymphoblastic</td>
</tr>
<tr>
<td>‒ Increased susceptibility to infection</td>
</tr>
<tr>
<td>‒ In patients surviving into middle age, morphologic changes in the brain similar to those of Alzheimer disease</td>
</tr>
</tbody>
</table>

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33. Developmental and Genetic Factors in Disease: Slide 33

Down syndrome – trisomy 21

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34. Abnormalities of Autosomal Chromosomes

Abnormalities of Autosomal Chromosomes

• Prenatal diagnosis of Down syndrome
  – Maternal lab “triple” screening:
    • Performed at 15-20 weeks gestation
    • 75% detection rate
    • 8.5% false positive rate
      – Low levels of serum alpha-fetoprotein and unconjugated estriol
      – High levels of hCG
  – Positive screening must be confirmed
    • Amniocentesis
    • Chorionic villus sampling (CVS)
    • Percutaneous umbilical blood sampling (PUBS)
35. Abnormalities of Autosomal Chromosomes

Abnormalities of Autosomal Chromosomes

- **Cri-du-chat syndrome (cry of the cat)**
  - Caused by deletion of the short arm of chromosome #5
  - Distinctive phenotype
    - Severe mental retardation, microcephaly, and an unusual catlike cry, low birth weight, round face, wide-set eyes, low-set ears, epicanthal folds
  - Very short life span

- **DiGeorge / velocardiofacial syndrome**
  - Caused by microdeletion of chromosome #22q11
  - Spectrum of clinical abnormalities
  - ‘CATCH 22’ syndrome
    - Cardiac abnormalities
    - Abnormal facies
    - T cell deficit because of thymic hypoplasia
    - Cleft palate
    - Hypocalcemia secondary to hypoparathyroidism

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36. Abnormalities of Autosomal Chromosomes

Abnormalities of Autosomal Chromosomes

- **Edwards syndrome (trisomy 18; 47,XX/XY+18)**
  - Most frequently results from nondisjunction resulting in trisomy 18
  - Marked by mental retardation, prominent occiput, micrognathia, low-set ears, rocker-bottom feet, flexion deformities of the fingers (index overlapping third and fourth), and congenital heart disease
  - Rare; very short life span

- **Patau syndrome (trisomy 13; 47,XX/XY+13)**
  - Manifest by mental retardation, microcephaly, microphthalmia, brain abnormalities, cleft lip and palate, polydactyly, rocker-bottom feet, and congenital heart disease
  - Rare; very short life span

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37. Common Autosomal Trisomies

Common Autosomal Trisomies

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38. Abnormalities of Sex Chromosomes

Abnormalities of Sex Chromosomes

- **Klinefelter syndrome**
  - Occurs when there are at least two X chromosomes and one or more Y chromosomes
  - Always is manifest by a male phenotype with testes
  - Most often characterized by the karyotype 47,XXY
    - A single Barr body is noted in buccal smear preparations
  - Variants include additional X chromosomes (e.g., XXXY) and rare mosaic forms
  - Most often caused by maternal meiotic nondisjunction
    - Incidence rises with maternal age

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39. Developmental and Genetic Factors in Disease: Slide 39

Abnormalities of Sex Chromosomes

- Klinefelter syndrome
  - Clinical findings
    - Most striking clinical changes are male hypogonadism and its secondary effects
      - Atrophic testes with infertility; hip female-like; lack of beard, body hair, pubic hair
    - Mental retardation
    - Tall stature; long arms and legs
    - Eunuchoid appearance with gynecomastia
  - Laboratory findings
    - Decreased testosterone production
    - Increased pituitary gonadotropins from loss of feedback inhibition

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40. Developmental and Genetic Factors in Disease: Slide 40

Abnormalities of Sex Chromosomes

- Turner syndrome
  - Occurs when there is complete or partial monosomy of the X chromosome
  - Most often characterize by an XO karyotype (45,X) in which no Barr bodies are seen on buccal smear
  - Clinical findings
    - Most striking clinical changes are female hypogonadism and its secondary effects
      - Replacement of the ovaries by fibrous streaks
      - Infantile genitalia and poor breast development
      - Most common cause of primary amenorrhea

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41. Abnormalities of Sex Chromosomes

Abnormalities of Sex Chromosomes

- Turner syndrome
  - Clinical findings (cont’d)
    - Short stature (avg. = 4’7”), webbed neck, shield-like chest with widely spaced nipples and wide carrying angle of the arms
    - Low posterior hairline, heart-shaped face
    - Cubitus valgus (turned-in elbows)
    - Lymphedema of the extremities and neck
    - Coarctation of the aorta and other congenital malformations
    - Usually not complicated by mental retardation
  - Laboratory findings
    - Decreased estrogen production
    - Increased pituitary gonadotrophins from loss of feedback inhibition

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42. Klinefelter Syndrome - Turner Syndrome

Klinefelter syndrome - Turner syndrome

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43. Normal Karyotype

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44. Developmental and Genetic Factors in Disease: Slide 44

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Abnormalities Due to Increased Numbers of Trinucleotide Repeats

- **Triple repeat mutations**
  - Expansion of the number of tandem trinucleotide repeats in certain critical genes
  - The number of repeats often increases from generation to generation and is associated with earlier onset and more severe manifestations in successive generations (i.e., “anticipation”)
    - Ex. - Huntington’s disease
      - Manifests in adults
    - Ex. - Fragile X syndrome
      - Common cause of familial mental retardation

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Abnormalities Due to Increased Numbers of Trinucleotide Repeats

- **Fragile X syndrome**
  - Important cause of hereditary mental retardation
  - Frequency second only to Down syndrome
  - Caused by cytogenetically demonstrable defect on the long arm of X chromosome
    - \( \rightarrow \) chromosome breakage in vitro
  - Considered to be an X-linked disorder however the pattern of inheritance has unusual features
    - Both males and females can be asymptomatic carriers
  - Carriers have an increased number of ‘CGG’ tandem repeats in the 5’ untranslated region of the familial mental retardation gene

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47. Fragile X Syndrome

Fragile X syndrome

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48. Modes of Inheritance of Monogenic Disorders

Modes of Inheritance of Monogenic Disorders - Single Gene Mendelian Disorders

Autosomal dominant inheritance

– One heterozygous parent carries a gene associated with a phenotypic expression of the disorder and the other parent is normal
– One half of the children are expected to inherit the gene and are themselves heterozygotes who phenotypically manifest the gene
– Distribution of the phenotype is the same in both sexes
49. Modes of Inheritance of Monogenic Disorders

Modes of Inheritance of Monogenic Disorders - Single Gene Mendelian Disorders

• Autosomal dominant inheritance – cont’d
  ❖ One gene or allele is defective; the other complementary allele is normal
    • ‘A’ = abnormal dominant gene
    • ‘AA’ and ‘aa’ = homozygous, identical alleles
    • ‘Aa’ = heterozygous, non-identical alleles
  ❖ Mutations affect structural entities such as collagen or regulatory proteins
  ❖ Reduced penetrance and variable expressivity
  ❖ Onset of the defect may be later in life

50. Autosomal Dominant Pedigree

Autosomal Dominant Pedigree

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Autosomal Dominant Disorders

- Adult polycystic kidney disease
  - Most frequent hereditary renal disorder
  - Numerous bilateral cysts replace and ultimately destroy the renal parenchyma
  - Clinically manifests between ages of 30 and 50 years even though a congenital defect
  - Death usually occurs about age 50

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Autosomal Dominant Disorders

- Familial hypercholesterolemia
  - Genetic defect characterized by anomalies of receptors for low-density lipoprotein (LDL receptors)
  - Results in decreased transport of LDL cholesterol into cells → hypercholesterolemia and striking increase in incidence and earlier onset of atherosclerosis and its complications
  - Further manifested by xanthomas
    - Raised yellow lesions filled with lipid-laden macrophages in the skin and tendons

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53. **Autosomal Dominant Disorders**

**Autosomal Dominant Disorders**

- **Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)**
  - Rare disorder seen with increased frequency in certain populations (e.g., Mormon families of Utah)
  - Localized telangiectases of the skin and mucous membranes and by recurrent hemorrhage from these lesions
    - Multiple, small, dilated capillaries
    - Spontaneous bleeding of the nose, gastrointestinal and genitourinary tracts is a significant problem

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54. **Hereditary Hemorrhagic Telangiectasia**

**Hereditary Hemorrhagic Telangiectasia**

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55. Autosomal Dominant Disorders

**Autosomal Dominant Disorders**

- **Hereditary spherocytosis**
  - Caused by a variety of inherited defects of erythocyte membrane-associated skeletal proteins
  - Spheroidal erythrocytes are sequestered and destroyed in the spleen -> hemolytic anemia

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56. Autosomal Dominant Disorders

**Autosomal Dominant Disorders**

- **Marfan syndrome**
  - Defect of connective tissue with faulty scaffolding
  - Caused by deficiency of fibrillin
    - Glycoprotein constituent of microfibrils
  - Defects in skeletal, visual, and cardiovascular structures
  - Patients tall, thin, abnormally long legs and arms, arachnodactyly and hyperextensible joints
  - Frequent ectopia lentis
    - Dislocation of the ocular lens
  - Cystic medial necrosis -> aortic dilation with aneurysm of the proximal aorta, aortic valvular insufficiency and dissecting aneurysm of the aorta
  - Loss of connective tissue support may lead to mitral valve prolapse

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57. Marfan Syndrome – Aortic Media

Marfan syndrome – Aortic Media

Marfan  Normal

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58. Autosomal Dominant Disorders

Autosomal Dominant Disorders

- Neurofibromatosis (von Recklinghausen disease)
  - Type 1
    - Mutated NF1 gene (tumor suppressor gene) at #17 chromosome
      - Normally codes for GTPase-activating protein that facilitates the conversion of active ras-GTP to inactive ras-GDP
    - Multiple neurofibromas in skin, internal organs, oral cavity
    - Skeletal disorders
      - Scoliosis and bone cysts

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59. Autosomal Dominant Disorders

Autosomal Dominant Disorders

- **Neurofibromatosis**
  - **Type 1 - cont’d**
    - Increased incidence of other tumors
      - Pheochromocytoma, Wilms tumors, rhabdomyosarcoma, leukemia
    - Lisch nodules
      - pigmented iris hamartomas
    - Café au lait spots
      - large hyperpigmented macules of skin
    - Disfiguring with a potential for malignant change of the neurofibroma lesions
  - **Type 2**
    - Disorder on chromosome #22
    - Development of 8th nerve schwannomas

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60. Neurofibromatosis – Type 1

Neurofibromatosis – Type 1

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61. Autosomal Dominant Disorders

Autosomal Dominant Disorders

- **Tuberous Sclerosis**
  - Glial nodules and distorted neurons in the cerebral cortex
  - Seizures, mental retardation
  - Sebaceous adenomas
    - Facial skin lesions consisting of sebaceous (oil-producing) glands and connective tissue
  - Rhabdomyomas of the heart
  - Renal angiomyolipomas
    - Malformed blood vessels, smooth muscle, and fat cells

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62. Tuberous Sclerosis

Tuberous Sclerosis

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63. Tuberous Sclerosis

Tuberous Sclerosis

Rhabdomyoma

“Tuber”

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64. Autosomal Dominant Disorders

Autosomal Dominant Disorders

Von Hippel-Lindau disease
– Gene on short arm of chromosome #3
– Hemangioblastoma or cavernous hemangioma of the cerebellum, brain stem, or retina
– Adenomas
– Cysts of the liver, kidney, pancreas, and other organs
– Associated with remarkably increased incidence of renal cell carcinoma

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65. Autosomal Dominant Diseases

Autosomal Dominant Diseases

- Dentinogenesis imperfecta
  - Inherited disease with defective dentin
  - Pulp canals are sclerosed and greatly narrowed
  - Teeth appear grayish and opalescent
  - Affects 1 in 8,000 individuals
  - May also be seen in osteogenesis imperfecta
    - Inheritable bone disease with blue sclerae and brittle bones

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66. Dentinogenesis Imperfecta

Dentinogenesis Imperfecta

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Modes of Inheritance of Monogenic Disorders

- Single Gene Mendelian Disorders

- Autosomal recessive inheritance
  - Both parents are heterozygous who do not phenotypically manifest the disorder
    - Both alleles are defective (e.g., phenylketonuria)
    - ‘a’ designates the abnormal recessive gene
  - Age of onset is usually early in life
  - Clinical features are more uniform than in autosomal dominant
  - More likely to affect enzyme proteins
  - Disorders include most of the inborn errors of metabolism

- Autosomal recessive inheritance – cont’d
  - One in four of the parents’ children will be homozygous for the trait and in the case of disease states, will phenotypically manifest the disorder
  - One in four of the children will not inherit the trait
  - Two of the children will be heterozygotes
  - Distribution of the disordered phenotype is the same in both sexes
69. **Autosomal Dominant vs. Autosomal Recessive Inheritance**

<table>
<thead>
<tr>
<th>Autosomal Dominant (A = abnormal dominant gene)</th>
<th>Autosomal Recessive (a = abnormal recessive gene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa has the disease</td>
<td>aa has the disease</td>
</tr>
<tr>
<td>AA will not live</td>
<td>AA is normal, Aa is a symptomless carrier</td>
</tr>
<tr>
<td>Males and Females are equally affected</td>
<td>Males and Females are equally affected</td>
</tr>
<tr>
<td>At least 1 parent shows the disease</td>
<td>Both parents are Aa, they do not show the disease</td>
</tr>
<tr>
<td>Disease show in every generation</td>
<td>Disease skips generations</td>
</tr>
<tr>
<td>Many siblings show the disease, 50% if one parent has the disease</td>
<td>Fewer siblings show the disease; 25% chance if there are 2 carriers</td>
</tr>
<tr>
<td>Not transmitted by one without disease</td>
<td>Transmitted by a carrier; offspring of one with aa and normal parent will be carriers</td>
</tr>
<tr>
<td>Not associated with consanguineous marriages</td>
<td>Associated with consanguineous marriage</td>
</tr>
</tbody>
</table>

- **Alleles** = alternate forms of a gene, e.g., ‘A’ and ‘a’
- **Homozygous** = identical alleles, i.e., ‘AA’ and ‘aa’
- **Heterozygous** = non-identical alleles, i.e., ‘Aa’

70. **Autosomal Recessive Pedigree**

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71. Autosomal Recessive Disorders

Autosomal Recessive Disorders – Inborn errors of metabolism

- **Lysosomal storage diseases**
  - Inherited single gene abnormality
  - Group of disorders characterized by deficiency of a specific single lysosomal enzyme resulting in an accumulation of abnormal metabolic products - - - > cellular and, ultimately, organ damage
  1) Lipid storage diseases
     - Tay-Sachs disease, Gaucher disease, Niemann-Pick disease
  2) Mucopolysaccharidoses
     - Ex. - Hurler syndrome
  3) Glycogen storage disease
     - von Gierke disease, Pompe disease, Cori disease, McArdle syndrome

- **Disorders of carbohydrate metabolism**
  - Classic galactosemia, galactokinase-deficiency galactosemia

- **Disorders of amino acid metabolism**
  - Phenylketonuria, alkaptonuria, maple syrup urine disease

- **Cystic fibrosis**

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72. Lysosomal Storage Diseases - Pathogenesis

Autosomal Recessive Disorders – Inborn errors of metabolism

Lysosomal Storage Diseases - Pathogenesis

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73. Autosomal Recessive Disorders

Autosomal Recessive Disorders – Inborn errors of metabolism

Pathogenesis of Lysosomal Storage Disease

A. Normal lysosomes digest material included within lytic bodies
B. Lack of degradation enzymes leads to accumulation of metabolic residues within the lysosomes

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74. Lysosomal storage diseases

Autosomal Recessive Disorders – Inborn errors of metabolism

Lysosomal storage diseases

(1) ‘Lipid storage diseases’
- Deficiency of enzymes for breaking down complex lipids
- Lipids accumulate in cells causing degeneration and necrosis of parenchymal cells in major organs
  ➢ Tay-Sachs disease
  ➢ Gaucher disease
  ➢ Niemann-Pick disease

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Autosomal Recessive Disorders – Inborn errors of metabolism

Lysosomal storage diseases

- Tay-Sachs (amaurotic familial idiocy)
  - Most common form of gangliosidosis and occurs primarily in Ashkenazic (central European origin) Jewish descent
  - Deficiency of hexosaminidase A \(\rightarrow\) \(G_m2\) ganglioside accumulates esp. in neurons
    - CNS degeneration
    - Severe mental and motor deterioration
    - Blindness (amaurosis)
    - Cherry-red spot in the macula
    - Death before age 4

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Autosomal Recessive Disorders – Inborn errors of metabolism

Lysosomal storage diseases

- Gaucher disease
  - Disorder of lipid metabolism caused by deficiency of glucocerebrosidase \(\rightarrow\) glucocerebroside accumulates in cells of the mononuclear phagocyte system
  - Gaucher cells
    - Enlarged histiocytes with a distinctive “wrinkled tissue paper” cytoplasmic appearance
  - Type I
    - 80% of cases; in adults - normal life span possible hepatosplenomegaly, erosion of femoral head and of the long bones, mild anemia
    - Gaucher cells in liver, spleen, lymph nodes, and bone marrow
  - Type II
    - Infants; severe CNS involvement; death before age 1
  - Type III
    - Juvenile; less severe than type II; brain and viscera involved

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77. Lysosomal Storage Diseases

Lysosomal Storage Diseases

- Niemann-Pick disease
  - Deficiency of sphingomyelinase → sphingomyelin accumulates in macrophages
  - Diffuse ‘foamy histiocytes’
    - Contain sphingomyelin; proliforate in liver, spleen, lymph nodes and skin
  - Hepatosplenomegaly, anemia, fever, and sometimes neurologic deterioration
  - May also exhibit a cherry-red spot in the macula, similar to Tay-Sachs disease
  - Death typically by age 3
  - Enlarged lymphatic system and viscera

78. Lysosomal Storage Diseases

Lysosomal Storage Diseases

- Tay-Sachs - whorled membranes
- Niemann-Pick - foamy cytoplasm

- Gaucher - wrinkled tissue paper appearance

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79. **Lysosomal Storage Diseases**

### Lysosomal Storage Diseases

- **(2) Abnormal mucopolysaccharide metabolism (mucopolysaccharidoses)**
  - **Hurler syndrome**
    - Deficiency of alpha-L-iduronidase \( \rightarrow \) MPS heparan sulfate and dermatan sulfate accumulate in lysosomes of heart, brain, liver, other organs \( \rightarrow \) cells enlarge and appear “clear”
      - Progressive deterioration with death by age 10
      - Hepatosplenomegaly
      - Dwarfism
      - Gargoyle-like facies
      - Stubby fingers
      - Corneal clouding
      - Progressive mental retardation

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80. **Lysosomal Storage Diseases**

### Lysosomal Storage Diseases

- **(3) Glycogen Storage Diseases**
  - Group of disorders caused by defects in the synthesis or degradation of glycogen
  - **Von Gierke disease**
    - Glycogen storage disease type I – hepatorenal glycogenosis
    - Deficiency of glucose-6-phosphate \( \rightarrow \) glycogen accumulates in the cytoplasm, swelling tissues of liver and kidney
      - Hepatomegaly
    - Sometimes intractable hypoglycemia

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Autosomal Recessive Disorders

- Inborn errors of metabolism
  - Lysosomal storage diseases
    - Inherited single gene abnormality
    - Group of disorders characterized by deficiency of a specific single lysosomal enzyme resulting in an accumulation of abnormal metabolic products -> cellular and, ultimately, organ damage
      1) Lipid storage diseases
         - Tay-Sachs disease, Gaucher disease, Niemann-Pick disease
      2) Mucopolysaccharidoses
         - Ex. - Hurler syndrome
      3) Glycogen storage disease
         - von Gierke disease, Pompe disease, Cori disease, McArdle syndrome
  - Disorders of carbohydrate metabolism
    - Classic galactosemia, galactokinase-deficiency galactosemia
  - Disorders of amino acid metabolism
    - Phenylketonuria, alkaptonuria, maple syrup urine disease
  - Cystic fibrosis

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Disorders of Carbohydrate Metabolism - Galactosemia

- Classic galactosemia
  - Deficiency of galactose-1-phosphate uridyl transferase - -
    - accumulation of galactose-1-phosphate in many tissues
  - Failure to thrive, infantile cataracts, mental retardation, progressive hepatic failure leading to cirrhosis and death
  - Prevention – early removal of galactose from the diet

- Galactokinase-deficiency galactosemia
  - Much less frequent than classic type
  - Often marked by only infantile cataracts

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Mannosidosis - Deficiency of Mannosidase

Lipid-laden macrophages accumulating in and causing overgrowth of the gingiva

Disorders of Amino Acid Metabolism

Phenylketonuria (PKU)
- Most cases caused by mutation of the phenylalanine hydroxylase gene so the enzyme phenylalanine hydroxylase is lacking
- Failure of conversion of phenylalanine to tyrosine in the liver so high serum concentrations of phenylalanine -> neurotoxic and progressive cerebral demyelination with mental deterioration - death by 1 year of age
- Seizures, hyperactivity
Disorders of Amino Acid Metabolism

Phenylketonuria (PKU) – cont’d

- Minor pathways of phenylalanine so phenylpyruvic acid ('phenylketones') and phenylacetic acid accumulate - - - child’s urine
- Also, the tyrosine deficiency - - - -> lack of pigment hair, eyes, and skin
- Mousy or musty body odor from phenylacetic acid in urine and sweat
- Effective treatment is phenylalanine-free diet

Phenylketonuria

- Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine
- Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones
- Excess phenylalanine also inhibits the formation of melanin from tyrosine
Disorders of Amino Acid Metabolism

Alkaptonuria
- Incomplete metabolism of phenylalanine and tyrosine due to deficiency of homogentisic oxidase there is an accumulation of homogentisic acid
- Characterized by urine that turns dark and finally black upon standing
- Ochronosis with incapacitating ochronotic arthritis
- Dark pigmentation of fibrous tissue and cartilage

Ochronosis - Femoral Head

- Pale yellow pigmented cartilage and sometimes muscle, epithelium and connective tissue, sclera, mucous membranes of lip, and skin of the ears, face and hands
- Cartilage degeneration results in osteoarthritis, especially of the spine

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Disorders of Amino Acid Metabolism

• Maple syrup urine disease
  – Rare inborn error of metabolism
  – Caused by any of a number of defects in the proteins that make up
    the branched-chain alpha-keto acid dehydrogenase complex
  – Mental and physical retardation, feeding problems, and a maple
    syrup odor to the urine
  – High urinary levels of keto acids of leucine, isoleucine, and valine
  – Untreated results in mental and physical disabilities and often leads
    to neonatal death
  – Can be detected by newborn screening programs and can be
    minimized in severity when treated with protein-modified diets

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Autosomal Recessive Disorders

$v$ Cystic fibrosis (mucoviscidosis)
  – The most common lethal genetic disease among Caucasians
    • Most common autosomal recessive disorder in U.S.
  – Caused by mutations in cystic fibrosis transmembrane
    conductance regulator gene (CFTR) on midsection of long
    arm of chromosome #7 – codes for membrane protein so . .
    • Abnormal transport of chloride across cell membrane - - - > thick or
      viscous fluids particularly in the pancreas, bronchi and intestine
  – Malfunction of exocrine glands - - - > increased viscosity of
    mucus and increased chloride concentration in sweat and
    tears
    • Sweat test is important diagnostic procedure
  – Secretion by sweat gland of chloride and sodium normal but
    reabsorption by sweat ducts impaired

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Autosomal Recessive Disorders

Cystic Fibrosis (cont’d)
- Chronic pulmonary disease
  - Retention of viscid mucus -> secondary infection, recurrent bouts of pneumonia, severe chronic bronchitis, bronchiectasis, and lung abscess
  - Infection with *Pseudomonas aeruginosa* is common cause of death (early age possible)
- Pancreatic insufficiency
  - Deficiency of pancreatic enzymes -> malabsorption and steatorrhea
- Meconium ileus
  - Small-bowel obstruction in the newborn caused by thick, viscous meconium

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Cystic Fibrosis

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93. Cystic Fibrosis

Cystic Fibrosis

Dilated plugged ducts of the pancreas

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94. Modes of Inheritance of Monogenic Disorders

Modes of Inheritance of Monogenic Disorders - Single Gene Mendelian Disorders

- X-linked recessive inheritance
  - Recessive genes located on the X chromosome and not on the Y chromosome
  - Most frequently the female parent is a heterozygous carrier and the male parent is genotypically and phenotypically unaffected
    - All female children inherit the paternal X chromosome and become carriers
    - All male children are genotypically and phenotypically unaffected
  - Variant – male parent carries the affected gene on the X chromosome and the female parent is unaffected
95. Modes of Inheritance of Monogenic Disorders

Modes of Inheritance of Monogenic Disorders
- Single Gene Mendelian Disorders

- X-linked recessive inheritance
  - The affected X chromosome will be inherited by one in two children
  - Male children who inherit the affected X chromosome phenotypically manifest the disorder
  - Heterozygous female children are carriers
  - Usually, only males exhibit the disease
    - Ex. – hemophilia, muscular dystrophy, hypohidrotic ectodermal dysplasia

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96. X-linked Recessive Pedigree

X-linked Recessive Pedigree

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97. X-linked Recessive Disorders

X-linked Recessive Disorders

- **Hunter syndrome**
  - A lysosomal storage disease that is a form of mucopolysaccharidosis clinically similar to, but less severe than, Hurler syndrome
  - Caused by deficiency of L-iduronosulfate sulfatase so heparan sulfate and dermatan sulfate accumulate
  - Hepatosplenomegaly, micrognathia, retinal degeneration, joint stiffness, mild mental retardation, and cardiac lesions

- **Fabry disease**
  - Lysosomal storage disease that is caused by deficiency of alpha-galactosidase A with resultant accumulation of ceramide trihexoside in body tissue

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98. X-linked Recessive Disorders

X-linked Recessive Disorders

- **Classic hemophilia (hemophilia A)**
  - Relatively common; caused by mutations affecting the factor VIII gene (tip of long arm of the X chromosome)
  - Deficiency of coagulation factor VIII
  - Hemorrhage from minor wounds and trauma, bleeding form oral mucosa, hematuria, and hemarthroses - - - progressive crippling deformities

- **Lesch-Nyhan syndrome**
  - Deficiency of hypoxanthine-guanine phosphoribosyl transferase - - - impaired purine metabolism and excess production of uric acid
  - Gout, mental retardation, choreoathetosis, spasticity, self-mutilation and aggressive behavior
99. X-Linked Recessive

X-Linked Recessive

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100. Von Willebrand Disease

Von Willebrand Disease

Increased bleeding time; normal platelets; vWF gene is on chromosome #12

Source: TUSDM

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101. X-linked Recessive Disorders

X-linked Recessive Disorders

- **Muscular dystrophy**
  - Dystrophin, a protein normal to the sarcolemma, is lacking
  - Cells cannot adapt to stress which results in muscular wasting
  - Mainly in males

- **Hypohydrotic ectodermal dysplasia**
  - Mainly in males
  - Ectodermally-derived structures fail to develop
  - Intolerance to heat because of lack of sweat glands
  - Missing teeth (partial anodontia) and hair/eyebrows

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102. X-Linked Hypohydrotic Ectodermal Dysplasia

X-Linked Hypohydrotic Ectodermal Dysplasia

Source: TUSDM

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103. Modes of Inheritance of Monogenic Disorders

Modes of Inheritance of Monogenic Disorders
-Single Gene Mendelian Disorders

• Other modes of inheritance
  ❖ X-linked dominant
    • Rare; heterozygous females as well as hemizygous males phenotypically manifest the disorder
    • Ex. - hypoplastic amelogenesis imperfecta
      — However, this condition has multiple modes of inheritance including autosomal dominant, autosomal recessive, X-linked recessive and X-linked dominant

104. Hypoplastic Amelogenesis Imperfecta

Hypoplastic Amelogenesis Imperfecta

Source: TUSDM

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Modes of Inheritance of Monogenic Disorders - Single Gene Mendelian Disorders

- **Mitochondrial inheritance**
  - Mutations within genes constituting the mitochondrial genome
  - Since only the ova have this type of DNA and not the sperm it is transmitted by females only
    - Mitochondrial genes inherited exclusively by maternal transmission
  - Defects in enzymes related to oxidative phosphorylation
    - Ex – mitochondrial myopathy
      - Neuromuscular system, liver, kidney, and heart

Mitochondrial Inheritance Pedigree

- Inheritance only through maternal lines
- Affected males do not pass on the genes
107. Non-Classical Inheritance

Non-Classical Inheritance

**Mechanisms**
- **Point mutations**
  - One base or nucleotide is substituted for another
  - **Ex.** Sickle cell disease
    - CTC → CAC; GAG → GUG; glutamic acid replaced by valine
- **Frameshift mutations**
  - Insertion or deletion of one or more bases in a coding region of DNA
- **Large deletions**
  - Extensive segment of DNA is deleted so gene product or protein often is missing

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108. Polygenic (Multifactorial) Inheritance

Polygenic (Multifactorial) Inheritance

- More common than monogenic disorders
- Abnormalities of complex processes regulated by the protein products of two or more genes
- Environmental factors also play an important role in the modulation of the genetic defects
  - ‘Normal traits’ - height, eye color, intelligence
  - Diabetes mellitus, hypertension, ischemic heart disease, gout, schizophrenia, bipolar disorder, neural tube defects, dwarfism, cleft lip/palate, periodontal disease and some cancers
- Risk of occurrence of disease is higher in first-degree relatives and in subsequent pregnancies

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### Polygenic (Multifactorial) Inheritance

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### Polygenic (Multifactorial) Traits –

#### (Non-Mendelian Genetic Inheritance)

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Diseases</th>
<th>Discontinuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traits</td>
<td>Diseases</td>
<td>Diseases</td>
</tr>
<tr>
<td>Height</td>
<td>Hypertension</td>
<td>Cleft lip and palate</td>
</tr>
<tr>
<td>Intelligence</td>
<td>Diabetes</td>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td>Anencephaly</td>
</tr>
<tr>
<td>Skin color</td>
<td></td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Metabolic parameters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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111. Causes of Fetal Abnormalities

Causes of Fetal Abnormalities

• **Teratogens**
  - Agents that cause fetal abnormalities
    - For 75% of malformations the cause is idiopathic
    - For 25% malformation in which the cause is known
    - Most are genetic, affecting the cells of the embryo (< 8 weeks old) or fetus
    - Some are exogenous, so if avoided then abnormality can be prevented
      - Physical – e.g., radiation
      - Chemical – e.g., alcohol abuse
      - Microbial – e.g., rubella virus

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112. Fetal Abnormalities Caused by External Agents (Teratogens)...

Fetal Abnormalities Caused by External Agents (Teratogens)

- **Congenital anomalies**
  - Present at birth
  - Not inherited
  - No chromosomal abnormality

- **Examples**
  - Congenital heart disease
  - Cleft lip and palate
  - Pyloric stenosis
  - Intestinal atresia
  - Clubfoot
  - Dislocation of hip

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113. Cleft Palate

Cleft Palate

Source: TUSDM

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114. Enamel Hypoplasia Due to Maternal Toxemia

Enamel Hypoplasia Due to Maternal Toxemia

Source: TUSDM

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Fetal Abnormalities Caused by External Agents (Teratogens)

- Idiopathic
  - Most
- Ionizing radiation
  - No safe low dose
- Viral infections infect fetus in utero causing defects
  - Rubella – first trimester -> anomalies
  - Cytomegalovirus, herpes virus -> multiple birth defects
- Drugs
  - Thalidomide -> phocomelia
  - Diethylstilbestrol (DES) predisposes daughters to premalignant (dysplastic) uterine vaginal changes
- Alcohol
  - Fetal alcohol syndrome – growth and mental retardation, facial deformities, cardiac problems
- Cigarette smoking
  - Prematurity, abortions, low birth weight

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Fetal or Congenital Abnormalities from Teratogens

Strabismus = crossed; nystagmus = oscillation

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117. Methods of Prenatal Diagnosis

Methods of Prenatal Diagnosis

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118. Newborn Screening Tests

Newborn Screening Tests

- Nine metabolic disorders tested for at birth
  - Phenylketonuria (PKU)
  - Congenital hypothyroidism
  - Congenital adrenal hyperplasia (CAH)
  - Biotinidase deficiency
  - Maple syrup urine disease
  - Galactosemia
  - Homocysteinuria
  - Sickle cell anemia
  - Medium chain acyl-CoA dehydrogenase deficiency (MCAD)

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