Genetic disorders

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What is genetics?
► Genetics = a diverse subject concerned with variation and hereditary in all living organisms
► Cytogenetics = the study of chromosome
► Molecular genetics = the study of the structure and function of individual genes
► Genomics = the study of genome, its organization, interaction and functions

Why is genetics important?
► Human diseases (classification)
  • Genetically determined
  • Environmental & genetically determined
  • Environmentally determined

Hereditary & Congenital
► Hereditary = derived from one's parents and transmitted in the germ line through the generations (=familial)
► Congenital = born with (inborn)
  • Congenital but not genetic = congenital syphilis
  • Genetic but not congenital = Huntington disease

Genetic disorders
► Classification
  • Single-gene disorders
  • Chromosome disorders
  • Multifactorial disorders
  • Somatic cell genetic diseases: Cancer

Genetic disorders
► Single-gene defects:
  • Caused by individual mutant genes
  • Usually exhibit characteristic pedigree patterns
  • Thalassemia, sickle-cell anemia, hemophilia
► Chromosome disorders:
  • Excess or a deficiency of the genes contained in whole chromosomes or chromosome segments
  • Trisomy 21 (Down syndrome), Turner syndrome
Genetic disorders

► Multifactorial inheritance
  ▪ The result of a combination of small variations in genes that together can produce or predispose to a serious defect, often in concert with environmental factors
  ▪ Tend to recur in family but show no characteristic pedigree pattern
  ▪ Affected 60% of population
  ▪ Diabetics, cancer, schizophrenia

Chromosomal disorders

► Trisomy 21 (Down syndrome)
  ▪ Occur 1 in 700 live birth
  ▪ Most common chromosomal disorders
  ▪ Mental retardation, protruding tongue, low-set ears, epicanthal folds, poor muscle tone, short stature, congenital heart anomalies (ASD), respiratory infection, leukemia

Down syndrome

► Associated with advanced maternal age
► 20% → paternal origin
► Extra 21st chromosome
► 4% → chromosomal translocation of long arm (inherited)

Trisomy 18 and 13

► Trisomy 18 (Edwards syndrome)
► Trisomy 13 (Patau syndrome)
  ▪ Less common than trisomy 21
  ▪ More severe
  ▪ Mental retardation, alive a few weeks after birth, congenital anomalies
Klinefelter syndrome
► Occur 1 in 850 live births
► Extra X chromosome (XXY, XXXY, XXXXY male phenotype)
► Abnormal sexual development and feminization (testicular atrophy, infertility, tall stature, gynecomastia, impaired intelligence)

Turner syndrome
► Monosomy X (X female phenotype)
► 1 in 3000 female births
► Short stature, webbing of neck, fibrous ovaries, sterility, amenorrhea, wide chest and congenital heart defects

Mendelian single-gene disorders
► Location of affected gene
  - Autosomal vs sex chromosome
► Mode of transmission
  - Dominant vs recessive
► Majority → familial
► 10-15% → new mutation

Autosomal dominant disorders
► M and F equally affected
► Affected individual have an affected parent
► Unaffected individual do not transmit disease
► Offspring of affected individual have 1 in 2 chance of inheriting disease
Autosomal dominant disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td>Huntington disease</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis</td>
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<tr>
<td></td>
<td>Myotonic dystrophy</td>
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<tr>
<td>Urinary</td>
<td>Polycystic kidney dis.</td>
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<tr>
<td>Gastrointestinal</td>
<td>Familial polyposis coli</td>
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<tr>
<td>Skeletal</td>
<td>Marfan syndrome</td>
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<tr>
<td></td>
<td>Osteogenic imperfecta</td>
</tr>
<tr>
<td>Metabolic</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td></td>
<td>Fam. hypercholesterolemia</td>
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</tbody>
</table>

**Marfan syndrome**

- AD, 70-85% familial, 1:5000
- Extracellular glycoprotein (fibrillin-1) FBN1: 15q21
- Skeleton, eyes and CVS
- 500 FBN1 mutations
- Abnormal fibrillin-1 → dominant negative

- Unusually tall, long extremities
- Tapering fingers & toes
- Laxation of joint ligaments
- Long headed (Dolichocephalic)
- Prominent supraorbital ridges
- Kyphosis, scoliosis
- Pectus excavation (pigeon-breasted deformity)

- Bilateral subluxation & discoloration of lens (ectopia lentis)
- Aortic aneurysm & dissection
- Mitral valve prolapse & regurgitation

Autosomal recessive disorders

- M and F equally affected
- Most cases the disease not apparent in parents
- Both parents are carriers of mutant recessive gene
- Unaffected individual may transmit disease to offspring
Autosomal recessive disorders

System
Metabolic

Disorder
Albinism
Phenylketonuria
Galactosemia
Homocysteinuria
Glycogen storage dis.
Sickle cell anemia
Thalassemia
Cong. Adrenal hyperplasia
Neuro. muscular atrophy

Sex-linked disorders

► X-linked disorders
- Affected individuals are always males
- Affected fathers transmit gene to non of their sons but to all of daughters
- Unaffected males do not carry defective gene
- A carrier female has a 1 in 2 chance of producing an affected son and a 1 in 2 chance producing a carrier daughter
- Female rarely affected in homozygous state

Hemophilia A

► Bleeding disorder ass. With a deficiency of factor VIII
► Bleed easily and profusely from minor injuries

Prenatal diagnosis

► Invasive testing
  - Amniocentesis (15th-16th week)
  - Chorionic villi sampling (10th-12th week)
  - Cordocentesis (19th-21th week)
  - Preimplantation genetic diagnosis

► Noninvasive testing
  - Maternal serum alpha-fetoprotein (16th)
  - Maternal serum screen (15th-20th week)
  - Ultrasonography
  - Isolation of fetal cells from maternal circulation
Neoplasia

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Nomenclature

- **Neoplasia** = “new growth” “The development of neoplasms” [*neo-, neos = new*] [*plassein = to form*]
- **Neoplasm** = “A new and abnormal formation of tissue, as a tumor or growth” [*plasma = form, mold*]
- **Tumor** = “A swelling” “neoplasm”
- **Oncology** = “The study of tumors” [*oncos = bulk, mass*]
- **Benign vs. Malignant tumor** = "ไม่ร้ายแรง " vs. "ร้ายแรงหรือร้ายแรงเรื้อรัง"
- **Cancer** = Malignant neoplasm [*Karnikos = crab*]

Epidemiology

- 23% of all deaths
- Second leading cause of death
- 66% of cancer deaths in > 65 yo
- 50% 5-year survival with treatment
- Male: Prostate (common)/ Lung (death)
- Female: Breast (common)/ Lung (death)

![Graph showing the leading causes of cancer and their prevalence in both genders.](image)
Benign VS Malignant Tumors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Typical of tissue of origin</td>
<td>Anaplastic, abnormal cell size and shape</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Localization</td>
<td>Local, capsule</td>
<td>Infiltrative</td>
</tr>
<tr>
<td>Metastasis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Terminology

►Benign tumors: suffix -oma
- Gland → Adenoma
- Squamous cell → Squamous cell papilloma
- Fat → Lipoma

►Malignant tumors: suffix -carnoma, sarcoma
- Gland → Adenocarcinoma
- Squamous cell → Squamous cell carcinoma
- Fat → Liposarcoma

►Malignant tumors with -oma:
- Seminoma
- Lymphoma (Malignant lymphoma)
- Melanoma (Malignant melanoma)
- Mesothelioma (malignant mesothelioma)
- Hepatoma (Hepatocellular carcinoma)

►Mixed tumor: Fibroadenoma
►Teratogenous: Teratoma (dermoid cyst)
**Fundamental to the origin of neoplasms**

- Heritable (genetic) change
- Excessive & unregulated proliferation
- Neoplasms

**Genetic Mechanisms of CA**

- Altered expression of cellular genes
  - Nonlethal genetic damage $\leftrightarrow$ carcinogens
  - Proto-oncogenes
  - Tumor suppressor genes
  - DNA repair defect
  - Clonal expansion $\leftrightarrow$ carcinogens
  - Acquire new mutations $\rightarrow$ malignant properties

**Six hallmarks of cancer**

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory signals
- Evading apoptosis
- Etching tissue invasion & metastasis

**Proto-oncogenes**

- Proto-oncogenes $\rightarrow$ mutation $\rightarrow$ oncogenes
- Oncogenes $\rightarrow$ oncoproteins $\rightarrow$ promote autonomous cell growth
- Categories:
  - Growth factors (PDGF)
  - Receptors (EGFR)
  - Cytoplasmic signal molecules (K-RAS)
  - Nuclear transcription factors (c-myc)

**Tumor Suppressor Genes**

- Growth inhibitory signals
  - Rb gene: retinoblastoma, osteosarcoma
  - P53: most human cancers
  - BRCA-1/BRCA-2: breast & ovarian cancers
- 3% all breast cancer
- 80% familial breast cancer
- Evasion of apoptosis
  - Bcl-2
Carcinogenesis

► Carcinogenesis:
  ▪ Initiation: genetic mutation
  ▪ Promotion: growth promotion
  ▪ Progression: development of malignant behaviors

► Carcinogens:
  ▪ Complete carcinogen: initiation & promotion
  ▪ Incomplete carcinogen: promotion

Carcinogens

► Chemical:
  ▪ Benzo(a)pyrene (cigarette) → lung cancer
  ▪ Aflatoxin → hepatoma (liver)
  ▪ Nitrosamine → cholangiocarcinoma (liver)

► Radiation:
  ▪ UV light → skin cancer
  ▪ X-ray → leukemia, thyroid cancer

► Virus:
  ▪ EBV → lymphoma

Invasion and Metastasis

► Invasion of extracellular matrix
► Invasion into vascular
► Vascular dissemination
  ▪ Lymphatic → lymph nodes
  ▪ Blood vessels → distant organs
► Tumor implantation
  ▪ Favoring location → homing

Tumor markers

► Substances associated with tumor cells that may indicate the presence of tumor
  ▪ Alpha fetoprotein (AFP) → liver cancer
  ▪ PSA → prostate cancer

► Immunohistochemistry:
  ▪ HMB-45 → melanoma
  ▪ C-kit (CD117) → GIST
  ▪ C-berb-B2 (HER2) → breast cancer

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Grading and Staging

- Grading: histologic characterization of tumor cells and is basically a determination of the degree of anaplasia (grade 1, 2, 3, 4)
- Staging: location and pattern of spread of a tumor within the host
  - International Contre Center → TNM (tumor, Node, Metastasis)
  - American Joint Committee → Stage 0 - IV

Effects of cancer on body

- Location & impingement on adjacent structures
- Functional activity such as hormone
- Bleeding & secondary infections
- Initiation of acute symptoms (rupture, infarction)

Effect of cancer on body

- Cachexia: overall weight loss and generalized weakness
  - Anorexia (loss of appetite)
  - High metabolism by cancer cells
  - Therapeutic effect → nausea, vomiting
- Pain: patient-controlled analgesia
- Psychosocial and family effect
- Paraneoplastic syndromes: acanthosis nigricans, venous thrombosis, cushing syndrome, hypercalcemia

Cancer Therapy

- Surgery: localized resectable cancer
- Radiation therapy:
  - Localized: unresectable mass
  - Total-body irradiation: bone marrow transplantation
- Chemotherapy: systemic administration
- Immunotherapy: interleukin, interferon
Risk factors

► Tobacco use:
  • Lung, larynx, oral, esophagus, pancreas, cervix, bladder
► Food:
  • Low fiber, high calories, red meat → colon CA
  • Antioxidants (Vit. A, E, C) → protective
► Alcohol:
  • Liver, oral, esophagus

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