Genetic Disorders

SCBM341: General Pathology

Amornrat N. Jensen, Ph.D.
Department of Pathobiology
School of Science, Mahidol University
amornrat.nar@mahidol.ac.th

Genetic disorders

• An illness caused by abnormalities in genes or chromosomes

• Genetic abnormalities maybe inherited, acquired during embryogenesis, or acquired later in life
Genes

• Double-stranded molecules of DNA

• Four types of nucleotide base
  - Adenine, Thymine, Cytosine, and Guanine

• Cells store the hereditary information in DNA

DNA is packaged in a chromosome

Chromosome

Human  Cells  Chromosomes (in nucleus)  A gene on a chromosome

Human has 46 chromosomes (23 pairs)

- One chromosome of each pair is inherited from mother and one from father
- Chromosomes other than the sex chromosomes called autosomes

Products of genes are specific proteins

- Proteins are essential molecules for living organisms
DNA codons are the code for each amino acid

The genetic code for amino acids is a triplet code

1 codon = 1 amino acid
Genetic mutations

- Permanent changes in the DNA

Example of genetic mutation

<table>
<thead>
<tr>
<th>CAC</th>
<th>CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>Glutamine</td>
</tr>
</tbody>
</table>

Normal protein | Faulty protein

Example: Mutation in β^0^-thalassemia

Kumar et al., Basic Pathology, 7th edition, 2003
Types of genetic disorders

1) Single gene / Mendelian disorders
2) Chromosomal disorders
3) Multifactorial / Complex disorders
4) Mitochondrial disorders

Single gene / Mendelian disorders

• Resulted from mutations in single genes

• Often have simple and predictable inheritance

• There are over 5,000 known mendelian disorders!
Transmission patterns of single gene disorders

1) Autosomal dominant

2) Autosomal recessive

3) Sex chromosome-linked

Dominant gene VS recessive gene

- Genes are always found in pairs that control the making of the same protein

- In some cases, one gene of the pair will control the feature
  - Gene that controls the feature: Dominant gene
  - The other gene in the pair: Recessive gene
Familial hypercholesterolemia

- The most common mendelian disorders (prevalence: 1 in 500)
- Caused by a mutation in gene encoded for LDL receptor
- LDL receptor functions in removing LDL from the blood circulation
- Patient with familial hypercholesterolemia has abnormally high level of LDL in the blood

Kumar et al., Basic Pathology, 8th edition, 2007
Transmission patterns of single gene disorders

1) Autosomal dominant

2) Autosomal recessive

3) Sex chromosome-linked

Autosomal recessive disorders

- The largest group of mendelian disorders

- The diseases occur only when both alleles of the genes are mutants

- Disease onset is usually early in life
Transmission pattern of autosomal recessive disorders

Sickle cell anemia

- A disorder that affects red blood cells
- Caused by a mutation in a gene encoding for beta subunit of hemoglobin
- Hemoglobin molecules do not form properly, causing red blood cells to be rigid and have a concave shape

http://learn.genetics.utah.edu
Transmission patterns of single gene disorders

1) Autosomal dominant

2) Autosomal recessive

3) Sex chromosome-linked

X-linked disorders

- There are relatively small number of x-linked diseases

- Almost all x-linked disorders are recessive

- Female carrying one mutant x allele usually does not carry a disease due to the presence of another normal allele

- Affected male does not pass x-linked trait to his son

http://genome.wellcome.ac.uk/doc_WTD020851.html
Transmission pattern of X-linked disorders

Red-green color blindness

- The most common form of color blindness
- Found in approximately 7% of male population in the US and only 0.4% of female population (Montgomery, Howard Huge Medical Institute)
- Caused by mutations in two genes that encode for red and green pigments
Types of genetic disorders

1) Single gene / Mendelian disorders

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Chromosomal Disorders

• Approximately 1 of 200 newborns has some form of chromosomal abnormalities

• Chromosomal disorders/ Cytogenetic disorders are caused by:
  1. Alterations in chromosome number
  or 2. Alterations in chromosome structure
Alterations in chromosome number

- **Nondisjunction** occurs when homologues fail to separate during meiosis

![Cell division diagrams showing nondisjunction](image)

- Trisomy cell has one extra chromosome
- Monosomy cell has one missing chromosome

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Down syndrome/ Trisomy 21

- Result of an **extra copy of chromosome 21**

![Karyotype diagram](image)

- Affects 1 in 800 children - the most common chromosomal disorder!
- Patients have characteristic facial features, short stature, heart defects, and short lifespan
Chromosomal abnormality

1. Alterations in chromosome number

2. Alterations in chromosome structure
   - Translocation
   - Deletion
   - Duplication

Diseases caused by chromosomal translocations
Disease caused by chromosomal deletion: Cri-du-Chat Syndrome

- Partial deletion of a small arm of chromosome 5
- Severe mental retardation
- People who have Cri-du-chat syndrome usually cry like a cat due to abnormal larynx development, have a small head, and unusual facial features

Types of genetic disorders

1) Single gene / Mendelian disorders
2) Chromosomal disorders
3) Multifactorial / Complex disorders
4) Mitochondrial disorders
Multifactorial or complex disorders

- Mutations in a number of genes, often coupled with an environmental influence (drug use, alcohol, pollutants etc.)

- Often cluster in families BUT do not have a clear-cut pattern of inheritance

- Low tendency to be inherited compared to single gene disorders

Example of complex multigenic disorders

- Asthma
- Diabetes
- Epilepsy
- Hypertension
- Coronary artery disease
Types of genetic disorders

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Mitochondrial disorders

- Mitochondria contain several copies of their own genetic material (mitochondrial DNA)
- Only egg contribute mitochondria to the embryo while sperm does not
- The DNA in mitochondria is inherited only from the mother
Transmission pattern of mitochondrial disorders

Examples of mitochondrial disorders

- Leber optic atrophy
  - Visual loss beginning in young adulthood

- Leigh's disease (Subacute Necrotizing Encephalomyelopathy)