The Role of Genetics in Medicine

- Clinical genetics
  - Genetic screening test
  - Prenatal diagnosis, newborn screening
  - Genetic counseling / ethics
  - Gene therapy

- First report in human genetics: Jewish report on hemophilia and gender transmission
- In 1865, Mendel published his work
- In 1956, the correct chromosome number was reported
- In January 1959, the chromosomal abnormality associated with clinical disorders was ever reported
- Mapping of genes to chromosomes and specific chromosome region, abnormal gene functions
Cystic Fibrosis Transmembrane Regulator, CTFR
The DNA sequence provided by the Human Genome Project (1988 – 2003)
- 3,095,784,273 base pairs with 32,020 genes

Approximately 3% of all pregnancies result in the birth of a child with a significant genetic disease or birth defect

Four major types of genetic disease:
- Single gene disorders
- Chromosomal disorders
- Polygenic or multifactorial diseases
- Somatic cell genetic disorders

Genes and Chromosomes
- Structure of DNA
- Central dogma
- Chromosomes
- Gene
- Cell cycle and cell divisions:
  - mitosis
  - meiosis
  - Mutation

Structure of DNA

“Central Dogma”

Transcription → Translation

Replication
Human Genome (chromosomes)

- In Nucleus: 3.1 x 10^9 bp
- In Mitochondria: 16,569 bp

- Gene 10%
- Non-gene (Extrageneric) 90%

  - Coding Sequences (Exon) <10%
  - Non-coding Sequences (Intron) 50%
  - Repetitive DNA 50%
  - Non-repetitive DNA 50%

  - Tandem repeats (satellite, minisatellite, microsatellite)
  - Interspersed repeats (SINES, LINES)

Cell cycle

- S: Replication of cell's genetic material
- G2: Cell growth
- M: Mitosis
- G1: Cell growth

- Can be divided into phases:
  - Interphase (G1, S, G2)
  - Mitosis (M)
  - G2 phase is the longest phase in the cell cycle.
Cell division

- Mitosis
- Meiosis and gametogenesis
- Crossing over
Mutation

- Mutation refers to the process that gives rise to changes in the DNA molecule.
- "Wild type" and "mutant allele"
- Normal variation, polymorphism, inherited disease
- Types of mutation
  - Base substitution => silent mutation, missense, nonsense
  - Insertion => frameshift mutation
  - Deletion => frameshift mutation
  - Chromosomal abnormality

Genetic disorders

- Single gene disorders
  - Mendelian inheritance
  - Non-Mendelian inheritance
- Chromosomal disorders
- Polygenic or multifactorial disorders
- Somatic cell genetic disorders
I. Single gene disorders

- Terminology
- Mechanism of mutation
- Functional effects of mutation on protein
- Mendelian inheritance of single gene disorders

Terminology

- **Genotype** = genetic constitution of an individual
- **Phenotype** = observed characteristic
- **Homozygote** = identical alleles at a given locus
- **Heterozygote** = two different alleles at a given locus
- **Autosomes** = any chromosomes other than sex chromosomes
- **Autosomal inheritance** = involve any chromosomes other than sex chromosomes
- **Pedigree charts** = to illustrate the inheritance

Terminology

- **Locus** = position of DNA sequences, or gene on a chromosome
- **Allele** = possible alternative form of a given gene
- **DNA polymorphism** = the occurrence in a population of two or more alternative genotypes
- **Gene pool** = the study of frequency of total alleles on a given locus
- **Population genetics** = the study of the genetic composition of populations
Introduction

- Single gene disorders are caused by individual mutant genes.
- There are approximately 11,000 single gene disorders, affecting 1% of the populations.
- Follow Mendelian patterns of inheritance:
  - Autosomal dominant inheritance (AD)
  - Autosomal recessive inheritance (AR)
  - X-linked recessive inheritance
  - X-linked dominant inheritance
  - Y-linked (Holandic) inheritance

Mendelian Inheritance

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- X-linked recessive inheritance
- X-linked dominant inheritance
- Y-linked (Holandic) inheritance
A “dominant phenotype” is one that is expressed in heterozygotes, whereas a “recessive trait” is expressed only in homozygotes.

If the expression of each allele can be detected in the presence of the other, the two alleles are termed “co-dominant.”

Autosomal Dominant

- Phenotypically expressed in homozygotes and heterozygotes for that gene
- There is vertical inheritance (affected child usually has an affected parent)
- Unaffected family members usually have unaffected partners, and they produce normal children
- Affected family members, usually have unaffected partners, and they produce a 1:1 ratio of normal and affected children
- Usually both sexes are equally affected, and they are equally likely to pass on the disease

Achondroplasia
Marfan syndrome

Examples

- **Skeletal**: Marfan syndrome, Achondroplasia, Osteogenesis imperfecta
- **Nervous system**: Huntington disease, Neurofibromatosis
- **Urinary**: Polycystic kidney disease
- **Gastrointestinal**: Familial polyposis coli
- **Hematopoietic**: Von Willebrand disease
- **Metabolic**: Familial hypercholesterolemia, Acute intermittent porphyria

Autosomal Recessive

- Expressed only in homozygotes, otherwise can be trait
- There is horizontal inheritance (normal parents often have more than one affected child)
- Affected individuals have phenotypically normal parents
- Affected individuals usually have unaffected partners and all their children will be carriers
• If a carrier has an unaffected partner, there is a 50% chance of the children being carriers
• Only mating between heterozygotes (carrier) will produce affected individuals, with an expected frequency of 1 in 4
• There is an association with consanguinity due to sharing of genes in families (rare recessive genetic disorders are more likely to arise through consanguinity)
• Both sexes are equally affected and equally likely to pass the mutation to the next generation
X-linked Dominant

- Rare, and difficult to distinguish from AD except that affected males have normal sons, but all daughters are affected
- Example: X-linked hypophosphatemic rickets, Rett syndrome

Example

- **Metabolic:** Cystic fibrosis, Phenylketonuria, Hemochromatosis, Glycogen storage disease, Galactosemia, Homocystinuria
- **Hematopoietic:** Thalassemia, Sickle cell disease
- **Endocrine:** Congenital adrenal hyperplasia
- **Nervous:** Friedreich ataxia
X-linked Recessive

- Many more males than females show the recessive phenotype
- The disease is transmitted by a carrier female, who is usually asymptomatic
- If a mother is a carrier, her son have a 50% chance of being affected and her daughters a 50% chance of being carriers
- An affected male will usually have no affected offspring, but all his daughters will be carriers and, in turn, 50% of their sons will be affected
- No sons of the affected male will inherit the gene (there is no male-to-male transmission)

Females do not tend to show X-linked recessive disease. However, woman can be affected in the following condition:

- If she is the daughter of an affected male (X^Y) and a carrier female (X^OX)
- If there is X chromosome-autosome translocation
- If 45,X (Turner syndrome) is present
- If greater proportion of normal X chromosomes are inactivated

[Diagram of Pedigree 7: X-linked recessive inheritance]

[Duchenne muscular dystrophy]
Example

- **Musculoskeletal**: Duchenne muscular dystrophy, Becker muscular dystrophy
- **Blood**: Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Hemophilia A and B
- **Metabolic**: Diabetes insipidus, Lesch-Nyhan syndrome
- **Nervous**: Fragile-X syndrome
- **Immune**: Agammaglobulinemia

II. Chromosomal Abnormalities

- Terminology
  - **Introduction**
  - **Numerical Chromosome abn.**
  - **Structural chromosome abn.**
  - **Chromosome instability synd.**

Terminology

- **Karyotype** = the chromosome constitution of an individual, normal human karyotype is 46,XY (male) and 46,XX (female)
- **Polyploidy** = the number of haploid chromosome sets is greater than two (2n), triploidy, tetraploidy
- **Aneuploidy** = chromosome number is not an exact multiple of haploid number, monosomies, trisomies
- **Trisomy** = three representatives of a given chromosome, trisomy 21 in Down syndrome
- **Monosomy** = one member of a chromosome pair is missing, Turner syndrome (45,X)
- **Translocation** = the transfer of one segment of a chromosome to another
Spectral Karyotyping (SKY) Analysis
Introduction

- Maybe numerical or structural
- Nomenclature
- Numerical disorders: [47, XY,+21], [45,X]
- Structural disorders: [46,XY,t(14;21)(q11,p10)], [46,XY,dup(5) (q20-q30)], [46,XY,del(15)(q11-q13)], (break point, margin, or region)

Numerical Chromosome Abnormalities

- Concern: Extra single chromosome, Missing single chromosome, Extra haploid sets
- Mechanisms
  - Polyploidy
  - Trisomies
  - Monosomies

Polyploidy

- Fertilization by two sperm
- A diploid sperm due to failure in meiosis
- A diploid ovum due to failure in meiosis

Trisomies

- Failure of separation (nondisjunction) of homologous chromosomes at meiosis I
- Failure of separation of chromatids in meiosis II
- Advancing maternal age is associated with increased incidence of trisomy
Monosomies

- Result from nondisjunction
- From “anaphase lag” = delay in movement of one chromosome to reach the pole of the cell before the nuclear membrane reforms during anaphase

Examples

- **Autosomal disorders:**
  - Trisomy 21 (Down syndrome)
  - Trisomy 18 (Edwards syndrome)
  - Trisomy 13 (Patau syndrome)

- **Sex chromosome disorders:**
  - Klinefelter syndrome (47,XXY)
  - Turner syndrome (45,X)
  - XXX = female with an extra X chromosome
  - XYY = male with an extra Y chromosome
  - **XX male** = Y sequences are transferred to the X chromosome, look like male with Klinefelter syndrome
Down’s syndrome

- CVS: Endocardial cushion defect (Atrioventricular septal defect) most common
- GI: increase risk of Hirschprung’s diseases (intestinal stenosis)
- Down’s syndrome facies
- Simian crease
- Gap between 1st and 2nd toes

Trisomy-13
Patau syndrome
Trisomy D
Polydactyly, CL/CP

Trisomy-18
Edwards syndrome
Trisomy E
The XYY Man is Spider Scott (Stephen Yardley), a burglar with an extra “Y” chromosome - which makes him predisposed towards crime. So when he's tapped up fresh out of prison by British intelligence to do a big job for a big price, he agrees to - which leads to a chain of events that threatens his life - and indeed other people's lives.

It's one of those 70s plots that involves various secret agents from several different countries - South Africa, Rhodesia (it still existed) and China in particular.
Structural Chromosome Abnormalities

- Result from breakage and limitations of DNA repair systems

Mechanisms
- Translocation
- Inversion
- Duplication
- Deletion and ring chromosome
- Isochromosome

Examples
- Prader-Willi syndrome and Angelman syndrome: deletion on 15q11-13
  - Prader-Willi: inheritance of the deletion from the father
  - Angelman: inheritance of the deletion from the mother
- Cri du chat syndrome (cat-like cry): Deletion of the region on 5p15.2 or the whole short arm of chromosome 5
Examples

- Prader-Willi syndrome and Angelman syndrome: deletion on 15q11-13
- Prader-Willi: inheritance of the deletion from the father
- Angelman: inheritance of the deletion from the mother
- Cri du chat syndrome (cat-like cry): Deletion of the region on 5p15.2 or the whole short arm of chromosome 5

mental retardation, low birth weight, low set ears, cat-like cry
III. Multifactorial Disorders

- Terminology
- Multifactorial disorders
- Threshold model of multifactorial disorders
- Examples of multifactorial disorders

Terminology

- Polygenic inheritance: the inheritance of traits that are influenced by many genes at different loci
- Multifactorial disorder: disorder in which both environmental and genetic factors are important

Multifactorial Inheritance

- Normal human characteristics: Blood pressure, height, finger ridges, and intelligence
- Congenital malformations: neural tube defects, cleft lip and palate, and congenital heart disease
- Common disorders of adult life: DM, Hypertension, peptic ulcer, and schizophrenia

Heritability and Environmental factors

- Heritability: percentage denoting that the genetic contribution of a given disease
  - If heritability is high, there is a high correlation in relatives
- Environmental factors: can be manipulated to reduce an individual’s susceptibility below than the threshold
Threshold model for Multifactorial disorders

Example

- Diabetes mellitus, type I (Insulin-dependent)
- Essential hypertension (62% heritability)
- Atherosclerosis (65% heritability)
- Peptic ulcer (37% heritability)
- Schizophrenia (85% heritability)
- Asthma (80% heritability)
- Alzheimer disease

Clinical genetics

- Genetic testing
- Prenatal diagnosis, newborn screening
- Genetic counseling / ethics
- Gene therapy
Genetic Testing for Carrier Detection

- To identify asymptomatic heterozygotes for AR traits, or AD disorders that have limited penetrance or late onset
- Confined to small ethnic populations in which there is an anomalously high incidence of a particular disease
- **Examples**: Thalassemia, Cystic fibrosis, ADPKD, Cascade screening

Prenatal diagnosis

- To assure of having unaffected children when the risk of having an affected child is unacceptably high
- NOT equivalent to the assurance of having normal children, It does not address all possible birth defects
- **Noninvasive techniques**: ultrasonography, maternal serum screening
- **Invasive technique**: amniocentesis, chorionic villus sampling, cordocentesis
- DNA analysis (PCR, Southern blot), Cytogenetic analysis

![Ultrasound equipment](http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/1062.jpg)

![Cordocentesis](http://www.pennhealth.com/health_info/pregnancy/graphics/images/en/19177.jpg)

![Cordocentesis](http://www.pennhealth.com/health_info/pregnancy/graphics/images/en/19175.jpg)
Newborn screening

- To identify treatable genetic disorders such as phenylketonuria, galactosemia, maple syrup urine disease, and congenital adrenal hyperplasia in newborn infants

- Dietary management is usually an early intervention to eliminate clinical symptoms that would otherwise lead to severe disability, mental impairment, or death

- Prevalence, severity of a condition, availability, effectiveness of a treatment, and cost will determine which disorder will be screened
Inborn error of metabolism
- PKU, galactosemia

Hormonal abnormality
- congenital hypothyroidism
- congenital adrenal hyperplasia

Genetic Counseling / Ethics

- Indications for genetic counseling
- Information conveyed in genetic counseling
- The process of genetic counseling

Indications for Genetic Counseling

- Known or suspected hereditary disease in a patient or family
- Birth defects
- Mental retardation
- Advanced maternal age
- Family history of early onset cancer
- Recurrent pregnancy loss
- Teratogen exposure
- Consanguinity

Information Conveyed in Genetic Counseling

- The magnitude of the risk of occurrence or recurrence
- The impact of the disease on the patient and the family
- The possibility of modification of either the impact or the risk
- Anticipated future development
## The process of genetic counseling

- Establishing the diagnosis (most important)
- Presenting the risk in context
- Discussing options, communication, and support
- Other considerations

## Ethical Considerations in Genetic Counseling

- Consanguinity and incest
- Disputed paternity
- Confidentiality and conflicts of interest
- Respect for Autonomy
- Beneficence and Nonmaleficence (do no harm)
- Privacy and confidentiality
- Justice and Equity

## Examples of ethical issues

- The mating of the first-degree relatives
- Testing for identification of biologic father
- Prenatal diagnosis for determination of fetal sex, or congenital birth defects
- High risk experimental therapy in a gravely ill infant
- Loss of health insurance, or job because of a genetic predisposition

## Gene therapy

The treatment of a disease by addition, insertion, or replacement of a normal gene or genes

**Two possible strategies:**
- Germ-line gene therapy
- Somatic cell therapy

**Requirements:**
- The *gene involved* should be cloned and characterized
- The *specific tissue* to be targeted should be accessible and identified
- A safe and efficient *vector system* for the gene should be defined
- The scientific rationale for the gene therapy approach should be sound and the *perceived risks* commensurate with the potential benefits
Germ-line Gene Therapy

- Genetic changes would be introduced into every cell type, including the germ line
- Can be passed from generation to generation
- Considered unethical

Somatic Cell Gene Therapy

- The genetic modifications are targeted specifically to the diseased tissue
- Germ cells would continue to carry the mutant forms of the disease gene

Gene therapy

- The treatment of a disease by addition, insertion, or replacement of a normal gene or genes

Two possible strategies:
- Germ-line gene therapy
- Somatic cell therapy

Requirements:
- The **gene involved** should be cloned and characterized
- The **specific tissue** to be targeted should be accessible and identified
- A safe and efficient **vector system** for the gene should be defined
- The scientific rationale for the gene therapy approach should be sound and the **perceived risks** commensurate with the potential benefits
Vector system

- The vector system is the means by which DNA is delivered to the target cells

- Two main types of vector system
  - Physical (nonviral) vector systems: Liposomes
  - Viral vectors
    - Integrate into the genome: retroviral, lentiviral, adeno-associated virus (AAV)
    - Maintained as an episome: adenovirus
Therapeutic strategies

- Selecting which genes to transfer and into what types of target cells
- Two general approaches to deliver gene therapy vector to the patient
  - Ex vivo gene therapy
  - In vivo gene therapy
- The most obvious and direct strategy is the treatment of a recessive genetic deficiency with the replacement of the missing DNA sequence

Diseases which can potentially be treated by gene therapy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>LDL receptor abnormalities</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Factor VIII (A), Factor IX (B) deficiency</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CFTR mutations</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Phenylalanine hydroxylase deficiency</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>Dystrophin mutations</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Alpha- and beta-globin gene mutations</td>
</tr>
<tr>
<td>Cancer</td>
<td>Protooncogene and tumor suppressor gene mutations</td>
</tr>
</tbody>
</table>
References

- คัมภิรานนท์ อมรา, "พันธุศาสตร์มนุษย์ (Human Genetics), พิมพ์ครั้งที่ 2." เข้ารังสี เจมส์ แททร์ ฟิลด์ส, กรุงเทพมหานคร, 2546.
- บุญแสง วิชัย และคณะ, "ลายพิมพ์ดีเอ็นเอ จากสารพันธุกรรมสู่เทคโนโลยีพิสูจน์บุคคล." เข้ารังสี เจมส์ แททร์ ฟิลด์ส, กรุงเทพมหานคร, 2546.