SUB MODULE 1C

SUBJECT: LIFE CYCLE

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MALANG

2014

Learning objectives:

Students should familiar with the cellular and molecular basis of inheritance, and its impact to genetic diseases.

Introduction

Medical genetics occupies the principles of hereditary material, how it is transmitted and the pattern of inheritance until its relevance to clinical genetics. The aspect in this study will include genetic structure and regulation, the central dogma, pathology process (mutation) and its inheritance mode.

The hereditary material is called DNA present in the nucleus of the cell, while protein synthesis takes place in the cytoplasm. The molecular link between the DNA code of genes and the amino acid code of protein is RNA. The informational relationship among DNA, RNA, and protein are called **Central Dogma** of molecular biology. DNA directs the synthesis and sequence of RNA, RNA directs the synthesis and sequence of polypeptides, and specific proteins are involved in the synthesis and metabolism of DNA and RNA by transcription and translation processes. During synthesis phase (S-phase) of cell division, DNA replicate to transmit genetic information to the next generation. However, the copy error could happened along replication, transcription and translation process. the change in the genetic material is called **mutation**, which can affect on autosome or sex chromosome. Mutation can occur on base level or chromosomal level.

Mutation and Pattern of Inheritance

According to the mutation occur, there are three main categories of genetic disorders, 1) single gene, 2) chromosomal, and 3) multifactorial. The patterns of transmission of single gene disorders are often called **Mendelian**. Genes at the certain locus are called allele. The **genotype** person is genetic constitution at a single locus and the **phenotype** is the expression of genotype as a morphological, biochemical, or molecular trait which may be normal or abnormal. Single gene disorder is determined by a specific allele at a single locus on one or both of a chromosome pair because human has a pair of chromosome homolog (same number). When a person has a pair of identical alleles, it condition is called **homozygous**; when the allele are different, it called **heterozygous** or carrier. Single gene disorders are characterized by their patterns of transmission in families. The step to establish the pattern is to obtain information about the family history of the patient and to summarize the details in the form of a pedigree using standard symbols. The patterns of single gene disorders in pedigree depend on two factors:

1. The chromosomal location of the gene locus: autosomal or sex linked (in sex linked cases mostly the genes are on x chromosome)
2. The expression of the phenotype:
    a. **Dominant**, expressed even when only one chromosome of a pair carried the variant allele
    b. **Recessive**, expressed only when both chromosome of a pair carry a variant allele

Thus there are four basic pattern of single gene inheritance: Autosomal dominant, autosomal recessive, x-linked dominant, x-linked recessive.

Non-Mendelian Inheritance

A number of disorders do not follow basic pattern of Mendelian inheritance. The several different mechanisms have been recognized are the following:

1. New mutation, the sudden unexpected appearance of a condition arising as a result of a mistake occuring in the transmission of a gene. New dominant mutation have been associated with an increased age of the father. This condition could be bias with **non-penetrance** which affected person's parents are heterozygous for the mutant allele but so mildly and has not been

detected. Other explanation for new mutation is that the stated father is not the child's biological father or **non-paternity.**
e.g. achondroplasia, Duchenne muscular dystrophy

2. Anticipation, the tendency for some diseases to manifest at an earlier age and/or to increase in severity with each succeeding generation. Usually refers to unstable mutation like triple repeat
   e.g. myotonic dystrophy, Huntington's disease, fragile-X syndrome
3. Reduced penetrance, usully refers to dominant traits in heterozygotes. If a condition is expressed is less than 100% of persons who carry the mutant allele.
4. Variable expressivity, when the manifestation of a phenotype differs in people who have the same genotype.
5. Mosaicism, an individual or particular tissue of the body can consist of more than one cell type or cell line through an error occuring during mitosis at any stage **after conception**.
   a. Somatic mosaicism, not inherited
   b. Gonadal mosaicism, may be transmitted to the next generation and could recurrence condition in offspring from unaffected parents.
6. Uniparental disomy, an individual who inherit both chromosome homologues pair from only one of their parents.
   e.g. father with hemophilia having an affected son
7. Genomic imprinting, differing expression of genetic material dependent on the sex of the transmitting parent.
   e.g. Prader Willi syndrome, Angelmann syndrome
8. Mitochondrial inheritance/matrilineal inheritance, transmission of mutant allele in the mitochondrial DNA from affected mother to all children, none of the children from affected male will inherit the disease.

Chromosomal Abnormality

There are two types of chromosome abnormalities. These can be divided into numerical and structural, with a third category consisting of different chromosome constitutions in two or more cell lines (Table 1)

Table 1. Types of chromosome abnormality

Numerical	
Aneuploidy	Monosomy; trisomy; tetrasomy
Polyploidy	Triploidy; tetraploidy
Structural	
Translocation	Reciprocal; robertsonian
Deletions	
Insertions	
Inversions	Paracentric; pericenctric
Rings	
Isochromosomes	
Different cell lines (mixoploidy)	
Mosaicism	
Chimerism	

Numerical abnormalities involve the loss or gain of **one or more chromosomes**, which is referred to as **aneuploidy,** or the addition of **one or more complete haploid complements**, which is known as **polyploidy**. In human triploidy is found relatively often in material from spontaneous abortion but survival beyond mid-pregnancy is rare. Only a few tripoid live births have been described and all

have died soon after birth. Loss of a single chromosome results in **monosomy**. Gain of one or two homologous chromosome is referred to as **trisomy** and **tetrasomy** respectively. Aneuploidy is usually caused by failure of separation of one of the pairs of homologous chromosomes during anaphase of meiosis I. This failure of the bivalent to separate is called **non-disjunction**. Less often, trisomy can be caused by non-disjunction occuring during meiosis II when pair of sister chromatids fail to separate. Thus the gamete receives two homologous chromosomes (disomy), and if subsequent fertilization occurs a trisomic conceptus results. Non-disjunction can also occur during an early mitotic division in the developing zygote. This result in the presence of two or more different cell lines, a phenomenon known as **mocaicism**.

Studies using DNA markers have shown that most children with an autosomal trisomy have inherited their additional chromosome as a result of non-disjunction occuring during one of the maternal meiotic divisions. However, aneuploidy could involve autosomal or sex chromosome (Table 2).

Table 2. Parental origin of meiotic error leading to aneuploidy

Chromosome abnormality	Paternal (%)	Maternal (%)
Trisomy 13	15	85
Trisomy 18	10	90
Trisomy 21	5	95
45,X	80	20
47,XXX	5	95
47,XXY	45	55
47,XYY	100	0

The cause of non-disjunction is uncertain. The most favoured explanation is that of an ageing effect on the primary oocyte which can remain in a state of suspended inactivity for ulp to 50 years. The acculutating effects of wear and tear on the primary oocyte during the arresting phase (*dictyotene*) probably damage the cell's spindle formation and repair mechanism thereby predisposing to non-disjunction.

Abnormalities in chromosome structure follow a chromosome break and the reunion of the wrong segments of the chromosome. Ifthere is a loss or gain of chromosomal material (an **unbalanced rearrangement**) there can be significant clinical consequences. If there is no loss or gain of chromosomal material (a **balancedrearrangement**), then the individual is mentally and physically usually normal. However, there is an increased risk of having chromosomally abnormal offspring because individuals who carry balanced chromosome rearrangements may produce chromosomally **unbalanced gametes**.

Genetic Disease Testing

Chromosome studies on parents should be ordered if a child is found to have a structural chromosome abnormality (e.g., translocation, deletion, inversion, etc.) to rule out carrier status. However, aneuploidy such as trisomy 21 and monosomy X (Turner syndrome), mostly is caused by nondisjunction related to advantage maternal age and cause children carry 47 chromosome which written as 47,xx/xy (+21). As nondisjunction occurs sporadically at the time the egg or sperm is formed, it is assumed that the parents of these children have a normal chromosome complement.Each types of genetic disorders needs the difference tools for analysis. Principally, there are two main way to detect the origin of abnormality. Single-gene disorders are analyzed by **molecular testing**, although suspected chromosome disorders are establised by **chromosome analysis (karyotype)**. In the description of a karyotype the first item to be recorded is the total number of chromosomes, including sex chromosomes, followed by a comma (,). The autosomes are specified only when an abnormality is

present. Thus, the normal human karyotype is designated as follows: **46,XX or 46 XY**. The abnormality chromosome is given next. For example, male trisomy 21 is designated as 47,XY,+21.

Treatment in Genetic Diseases

In genetic diseases, there is special consideration in treating genetic diseases. The need for long-term assessment of treatment could appear some unexpected problems. For example, clotting factor infusion in hemophilia sometimes result in the formation of antibodies to the infused protein, and blood transfusion in thalassemia can produces iron overload, which can be managed but with difficulty.

Genetic disease can be treated at many levels as shown below. Treatment at the level of the clinical phenotype include all the types of medical or surgical intervention, for example some surgically correctable malformations (cleft lip/palate, vaginoplasty in androgen insensitivity syndrome/AIS, clitoridectomy in congenital adrenal hyperplasia/CAH or female virilisation), besides educating the patient and family to achieve understanding of the disease, its genetic implications, and the treatment that may be inconvenient and lifelong (Table 3).

Table 3. The levels of genetic disease treatment.

Level of intervention	Treatment strategy	Examples
Mutant gene	Modification of the somatic genotype (transplantation; gene transfer therapy)	Bone marrow transplantation in thalassemia
	Pharmacologic modulation of gene expression	Hydroxyurea to stimulate g-globin synthesis in sickle cell disease
Mutant mRNA		
Mutant protein	Protein/enzyme replacement	Factor VIII in hemophilia A
Metabolic or other biochemical dysfunction	Dietary or pharmacologic	PKU~dietary of phenylalanine Galactosemia~dietary of galactose CAH~hydrocortison Congenital hypothyroidism~thyroxine Fragile-x~minocycline
Clinical phenotype	Medical or surgical intervention	Cleft lip/palate, CAH, AIS
The family	Genetic counseling; carrier screening; presymptomatic diagnosis	All genetic disorders

Based on the technology used, treatment of genetic diseases is divided into two ways:

1. Conventional approaches; protein/enzyme, drug treatment, tissue removal/transplant
2. Using DNA recombinant; insulin synthesize from human insulin gene by microorganism
3. Gene therapy, the replacement of a deficient gene product or correction of an abnormal gene which can be done either in vitro by treatment of cells or tissue from an affected individual in culture with reintroduction into the affected individual, or in vivo if cells cannot be cultured or be replaced in the affected individual.

References:

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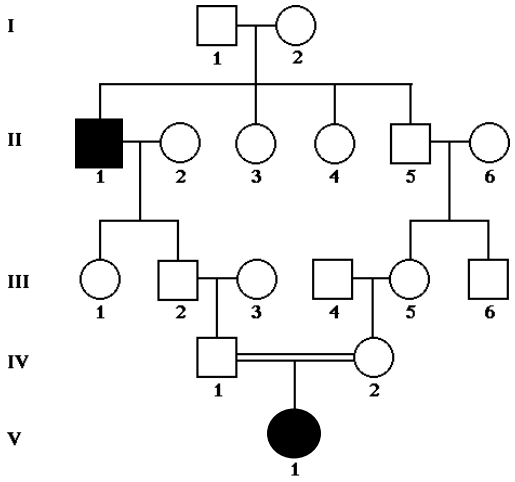
Mueller RF & Young ID. 2001. Emery's elements of medical genetics, 11th ed. Churchill Livingstone, London.
Pasternak JJ. An introduction to human molecular genetics: mechanisms of inherited diseases, 2nd ed., John Willey & Sons, New Jersey, 2005.
Shaffer LG, Slovak ML, Campbell LJ (eds). ISCN: An International System for Human Cytogenetic Nomenclature (2009), S. Karger AG, Basel, 2009.

Modul task:

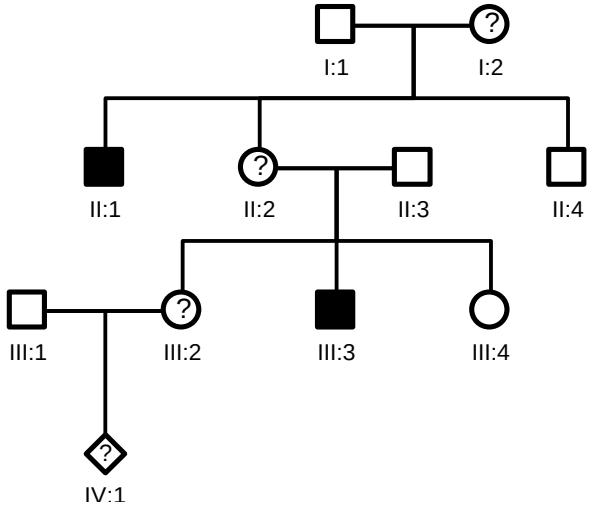
1. Does the mutation on base level change the chomosome structure? Explain your answer.
   Answer:

2. The disease in the pedigree below is inherited in what manner? Mention the **characteristic and sample of diseases**for this manner.



3. Why is it important to know your patient's ethnic background? Why should you ask about consanguinity?
   Answer:

4. From the pedigree, it was known that individual II:1 and III:3 have severe hemophilia A.
   a. What is the mode of inheritance of this disease? Give a reason for your answer!



b. Give the mark of the possibility genotype status below each individual!
   Answer:

c. The affected individual got the mutant allele from ..... explain your answer!

d. Based on the pedigree, the female who obligatory has mutant allele or carrier are ..... , then they are called an **obligate carrier**.

e. What is the chance for individual III:2 to be a carrier for haemophilia A?

f. The possibility of the pregnancy (IV:1) to be affected hemophilia <u>if his mother (III:2) is carrier</u> is .....

g. Give another samples of **trait or disease** on X-linked recessive manner.

5. Discuss the cause of triploidy in human and its consequences due to the additional set of chromosome come from (paternally or maternally).
   Answer:

6. What should you do if you have a patient with <u>suspect</u> Down Syndrome?
   Answer:

7. A newborn child with Down syndrome, when karyotyped, is found to have two cell lines: 70% of her cells have the typical 47,XX,+21 karyotype, and 30% are nomal 46,XX. When did the nondisjunctional event probably occur? What is the prognosis for this child?
   Answer:

8. Discuss possible reasons why the **recurrence risk** of Down syndrome is **higher** for mothers under 30 years of age than for mothers over 35 years of age.
   Answer:

9. What will you do to determine the sex status of suspected patient with development sex disorder in case ambiguous genitalia?
   Answer:

10. Buccal smear is not recommended to do as a sexual determination in case ambigous genitalis, why?
    Answer: