Histopathology 2

Lecture 2

Genetic Diseases

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Genetic Diseases

OVERVIEW

There are three major types of mutations: (1) genome mutations, which involve loss or gain of an entire chromosome; (2) chromosomal mutations, which involve alterations in one or more chromosomes that are usually identifiable by karyotyping; and (3) gene mutations, which are partial or complete deletion of the gene or alteration of the base. Genome mutations usually result in death of the fetus, or death during infancy or early childhood.

Many diseases have a genetic component, albeit without a specific identifiable gene mutation. Such conditions are said to have a multifactorial inheritance pattern. Examples of such diseases include coronary artery disease, hypertension, gout, and diabetes mellitus.

When discussing genetic diseases, some definitions are important to remember: (1) hereditary or familial, a condition derived from parents (i.e., a condition that is transmitted in the germ line); and (2) congenital, a condition that is present at birth. Not all hereditary conditions are congenital, and not all congenital conditions are hereditary. Some hereditary conditions are manifested at the time of birth or shortly thereafter, and many manifest later in life

The overall effects of the mutation of a single gene include **(1)** an enzyme defect; **(2)** defects in membrane receptors and/or transport system; **(3)** alterations in structure, function, or quantity of nonenzymatic protein; or **(4)** mutations resulting in unusual reactions to drugs.

AUTOSOMAL DOMINANT DISORDERS

Overview: In general, autosomal dominant disorders have reduced penetrance and variable expressivity. They usually do not encode enzymes because a loss of up to 50% of an enzyme's activity can be compensated for by activity of the enzyme encoded by the normal allele.

FAMILIAL HYPERCHOLESTEROLEMIA

Mutation: Low-density lipoprotein receptor gene (LDL); there are more than 100 known mutations.

Mechanism: The LDL receptor recognizes apolipoprotein B100 or apolipoprotein E; therefore, a mutation of the receptor results in impaired uptake of cholesterol into cells.

Manifestations of familial hypercholesterolemia

■ Elevated cholesterol level: Heterozygotes have half the normal amount of LDL receptors and two to three times the normal level of cholesterol; homozygotes have five or more times the normal level of cholesterol.

■ Early atherosclerosis and its consequences; homozygotes usually die of cardiovascular disease before the age of 30 years.

GALACTOSEMIA

Mutation: Gene for galactose-1-phosphate uridyltransferase (GALT), which is required to convert galactose to glucose.

Manifestations of galactosemia

■ Cirrhosis.

■ Opacification of the lens (cataracts)—due to accumulation of galactitol, the lens absorbs water and swells. ■

Mental retardation.

■ Aminoaciduria due to accumulation of galactose in the kidney, which impairs amino acid transport.

HEREDITARY HEMOCHROMATOSIS

Mutation: HFE gene on chromosome 6p21.3.

Epidemiology: 1 in 250 individuals of European descent are homozygous; incidence is higher in males than in females.

Mechanism: Increased intestinal absorption of iron leads to iron buildup in organs.

Manifestations of hereditary hemochromatosis

■ Bronze skin discoloration due to iron deposition.

■ Diabetes mellitus due to pancreatic fibrosis.

■ Cirrhosis of the liver.

■ Dilated or restrictive cardiomyopathy.

Clinical presentation: The classic triad of symptoms is arthralgia or arthritis, impotence, and fatigue.

SEX CHROMOSOME ABNORMALITIES

KLINEFELTER SYNDROME

Genetic abnormality: A male hypogonadism due to the presence of two or more X chromosomes and one or more Y chromosomes (82% of cases are 47,XX).

Incidence: 1 in 500 live births.

Mechanism: Increased level of follicle-stimulating hormone (FSH) and decreased level of testosterone.

Manifestations of Klinefelter syndrome :

■ Hypogonadism (atrophic testes and small penis) and sterility.

■ Tall stature due to increase in length between sole and pubic bone (long legs).

■ Reduced body hair.

■ Most have normal intelligence

.■ 20 times increased risk for breast carcinoma.

■ Barr body (inactive X chromosome).

FRAGILE X SYNDROME

Genetic abnormality: Trinucleotide (CGG) repeats on the X chromosome; affects FMR1 gene (Xq27.3).

Manifestations: Long face with large mandible; large testicles; mental retardation.

Diagnosis of Genetic Diseases

Early and accurate diagnosis is crucial for managing genetic diseases.

Diagnostic methods include:

A. Molecular Techniques

- **Polymerase Chain Reaction (PCR):** Amplifies specific DNA sequences to detect mutations.
- **Next-Generation Sequencing (NGS):** Analyzes entire genomes for genetic variants.
- **Sanger Sequencing:** Identifies specific mutations in a gene.

B. Cytogenetic Techniques

• **Karyotyping:** Detects chromosomal abnormalities by examining the structure and number of chromosomes.

• **Fluorescence In Situ Hybridization (FISH):** Identifies specific DNA sequences using fluorescent probes.

C. Biochemical Tests

• Measures enzyme levels or metabolic by products to diagnose metabolic disorders (e.g., phenylketonuria).

D. Prenatal and Newborn Screening

• **Amniocentesis:** Tests amniotic fluid for genetic abnormalities during pregnancy.

• **Newborn Screening:** Identifies genetic conditions early to initiate treatment (e.g., screening for sickle cell anemia).

Test yourself

Q\ A 10-year-old child presents with xanthomas on the extensor surfaces of his forearms. Laboratory studies demonstrate a total serum cholesterol of 820 mg/dL. The child's mother and maternal grandfather also have elevated serum cholesterol. This patient most likely has mutations in the gene that encodes which of the following proteins involved in lipid metabolism? And why?
(A) ApoE4
(B) Cholesterol hydroxylase
(C) Chylomicron transport protein
(D) High-density lipoprotein receptor
(E) Low-density lipoprotein receptor