**AL-FARABI KAZAKH NATIONAL UNIVERSITY**

***Faculty of Medicine and Healthcare, Higher School of Medicine***

***Department of Fundamental Medicine***

MZiB2216 "Mechanisms of Defense and Disease (medical genetics, medical microbiology, general pharmacology)"

**Lectures  of the Medical Genetics**

**Lecture 1-2**

***Introduction to Medical Genetics***

***Chromosomal disorders***

***Goal:***

Demonstrate knowledge and understanding of advanced knowledge in the field of Medical Genetics. Understand the mechanism of development of chromosomal diseases. Identify clinical features of autosomal chromosomal disorders, explain their genetic forms*.*

***Content:***

Classification of Hereditary diseases.

Chromosomal mutations: characteristics, cause, mechanisms, frequency, phenotypic manifestation, clinical significance.

Diagnosis and management of chromosomal disorders.

Epidemiology of chromosomal disorders.

Down syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Edward’s syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, prognosis, epidemiology.

Patau syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, prognosis, epidemiology.

Cri du chat syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, epidemiology.

Down syndrome (mongolism or trisomy 21) occurs when there are three copies of chromosome 21 as shown in the karyotype in figure. It is due to the presence of an extra chromosome 21. These individuals have 47 chromosomes (not 46) in all their body cells. Down’s syndrome was first reported in 1866 by Langdon Down but its cause was found in 1959 by Lejeune and his coworkers. Trisomy -21 occurs with a frequency of about 3.510 per 1 million conceptions and about 1.430 per 1 million live births. Mother’s around 45 years of age have a much higher risk of having infants with Down syndrome then the ones between 20-30 years.

Symptoms of Down syndrome:

● severe mental retardation. Short neck, flat hands.

● number of abnormalities in the facial structure are: prominent forehead, flattened nasal bridge, habitually open mouth, protruding lower lips, large generally protruding tongue, a characteristic fold of skin at the corner of the eyes, short and broad neck, flat hands, oval mongoloid face having superficial similarity to mongolians.

● malformation of heart.

● underdevelopment of gonads.

***Questions for control:***

1. Explain principles of classification of chromosomal disorders.
2. Identify clinical features of autosomal chromosomal diseases and explain their clinical variability.
3. explain genetic mutations as the cause of autosomal chromosomal disorders.
4. compare different diagnostic strategies for diagnosing autosomal chromosomal disorders and discuss related ethical and legal issues.
5. compare and contrast different management strategies for autosomal chromosomal disorders (prevention, treatment) and discuss related ethical and legal issues.
6. summarize epidemiologic data of chromosomal disorders.
7. discuss the impact of diagnosis of a genetic condition for the individual and the family.
8. demonstrate respect for the patient's religious, cultural, social and ethical beliefs and understanding of how that might affect the decisions the patients make.

***Recommended References:***

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**Lecture 3**

***Sex chromosome disorders***

***Goal:***

Demonstrate the understanding of mechanism of development of sex chromosome diseases. Identify clinical features of sex chromosome disorders, explain their genetic forms*.*

***Content:***

Sex chromosome disease characteristics, causes, mechanisms, frequency, phenotypic manifestation, clinical significance.

Diagnosis and management of sex chromosome disorders. Epidemiology of sex chromosome disorders.

Turner syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Klienfelter syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Triple X syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Jacob’s syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Hermaphroditism, its types.

Turner syndrome is caused by XO genotype. The individual has 45 chromosomes (2n-1) and is a sterile female with underdeveloped breasts, reduced ovaries, small uterus. Turner syndrome individuals occur with a frequency of 1 in 10.000 female births. It is estimated that up to 99 percent of all 45, X embryos die before birth. Surviving Turner syndrome individuals have few noticeable major defects until puberty, when they fail to develop secondary sexual characteristics. They tend to be shorter than average, and they have web-like necks, poorly developed breast, and immature internal sexual organs. They have a reduced ability to interpret spatial relationships and are usually infertile. Females are often sterile as they may not menstruate or ovulate, subnormal intelligence, with many male characteristics such as heavy neck muscles and narrow hips.

***Questions for control:***

1. identify clinical features of sex chromosome diseases and explain their clinical variability.
2. explain genetic mutations as the cause of sex chromosome disorders.
3. compare different diagnostic strategies for diagnosing sex chromosome disorders and discuss related ethical and legal issues.
4. compare and contrast different management strategies for sex chromosome disorders (prevention, treatment) and discuss related ethical and legal issues.
5. discuss the impact of diagnosis of a genetic condition for the individual and the family.
6. demonstrate respect for the patient's religious, cultural, social and ethical beliefs and understanding of how that might affect the decisions the patients make.
7. work with genetic databases (OMIM & etc).

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**Lecture 4-5**

***Mendelian classic disorders: autosomal inheritance***

***Goal:***

Demonstrate the understanding of autosomal inheritance, clinical features of autosomal-linked diseases*,* mechanism of gene mutation and mechanism of formation of enzymopathies.

***Content:***

Mendelian classic disorders: autosomal inheritance. Classifications, pathogenetic, pathogenetic mechanisms, epidemiology and management.

Classification of classic Mendelian disorders.

Gene mutations: characteristics, cause, mechanisms, frequency, phenotypic manifestation, clinical significance.

Diagnosis and management of classic Mendelian disorders. Epidemiology of single gene disorders, prognosis.

Cystic fibrosis: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Mechanism of formation of enzymopathies.

Phenylketonuria: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Galactosemia: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Alkaptonuria: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Fructosuria: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Marfan syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Achondroplasia: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Wilson-Konovalov disease: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Hypertrichosis: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Phenylketonuria (PKU)– is an inborn error of metabolism. PKU occurs in about 1 in 12.000 births. PKU is most commonly caused by a recessive mutation of a gene on chromosome 1. The homozygous recessive individual lacks the enzyme phenylalanine hydroxylase needed to change one amino acid, phenylalanine, to another, tyrosine. The absence of that enzyme activity prevents the conversion of the amino acid phenylalanine to the amino acid tyrosine. Phenylalanine, phenylketones and other derivatives in urine, in the tissues accumulate, and some of it into phenylpyruvic acid which damages the brain and causes the disease. Accumulation of derivatives affects the cells of the central nervous system and produces serious symptoms: severe mental retardation, a slow growth rate, and early death.

Galactosemiais a defect of metabolism sugar - lactose. Accumulation in blood galactose occurs, mental and developmental retardation, liver damages, nervous system, eyes and other organs. It is due to recessive mutation of genes. Autosomal-recessive type of inheritance. It is about 1 in 16.000 births.

***Questions for control:***

1. explain the mechanism of formation of monogenic disorders.
2. identify clinical features of autosomal-linked diseases.
3. compare different diagnostic strategies and principles of diagnosis of autosomal (dominant and recessive) monogenic disorders and discuss related ethical and legal issues.
4. summarize principles of management of autosomal (dominant and recessive) monogenic disorders (prevention, treatment) and discuss related ethical and legal issues.
5. identify the methods of diagnosis of enzymopathies.
6. discuss the impact of diagnosis of a genetic condition for the individual and the family.
7. demonstrate respect for the patient's religious, cultural, social and ethical beliefs and understanding of how that might affect the decisions the patients make.
8. work with genetic databases (OMIM & etc).

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**Lecture 6**

***Mendelian classic disorders: sex-linked inheritance***

***Goal:***

Demonstrate the understanding of sex-linked inheritance, clinical features of sex-linked diseases and its transmission.

***Content:***

Mendelian classic disorders: sex-linked inheritance. Classifications, pathogenetic mechanisms, epidemiology and management.

Hemophilia: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Color blindness: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Ichthyosis: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Lesch–Nyhan syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Duchenne Muscular Dystrophy: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Vitamin-resistant rickets: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

X-linked recessive type of inheritance: Affect the males more than the females; Females inherited the recessive trait only from father; More males than females should exhibit the trait; All sons of a homozygous mutant mother should show the trait, since males recessive their only X chromosome from their mothers; The sons of heterozygous (carrier) mothers should show an approximately 1:1 ratio of normal individuals expressing the trait. There is a 50 % chance that the son would get that disease/trait. X – linked recessively inherited trait is hemophilia.

X – linked dominant inheritance: a trait due to a dominant gene carried on the X chromosome is called an X – linked dominant trait. Only a few X – linked dominant traits have been identified. An example of an X – linked dominant trait that causes faulty tooth enamel and dental discoloration, also is a severe bleeding anomaly as constitutional thrombopathy, bleeding is not due to the absence of a clotting factor (as in hemophilia), but to inheritance in the formation of blood platelets, which are needed for blood clotting.

***Questions for control:***

1. explain the mechanism of formation of monogenic disorders.
2. identify clinical features of sex-linked diseases.
3. compare different diagnostic strategies and principles of diagnosis of sex-linked (dominant and recessive) disorders and discuss related ethical and legal issues.
4. summarize principles of management of sex-linked (dominant and recessive) disorders (prevention, treatment) and discuss related ethical and legal issues.
5. discuss the impact of diagnosis of a genetic condition for the individual and the family.
6. demonstrate respect for the patient's religious, cultural, social and ethical beliefs and understanding of how that might affect the decisions the patients make.
7. work with genetic databases (OMIM & etc).

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**Lecture 7-8**

***Non-mendelian genetic disorders***

***Goal:***

Demonstrate the understanding of non-mendelian genetic disorders, their clinical features and transmission.

***Content:***

Non-mendelian genetic disorders: causes, classifications, pathogenetic mechanisms, epidemiology, diagnosis and management.

Mitochondrial diseases.

Genomic imprinting.

Epigenetic of depression.

Trinucleotide Repeat disorders.

Huntington's Disease: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Prader-Willi syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Angelman syndrome: features and symptoms, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Prader-Willi syndrome. 30% of all cases are caused by uniparental maternal disomy and 70% is caused by deletion in the 15 chromosome (q11-q13) of paternal origin. Infants with this syndrome are weak because their sucking reflex is poor, making feeding difficult. As a result, growth is poor.

In early childhood, Prader-Willi syndrome is characterized by severe hypotension, feeding difficulties and hypogonadism with cryptorchidism. Muscle tone improves over time, although adults remain slightly pshotonic. Hypogonadism of hypothalamic origin does not improve with age and usually causes late and incomplete puberty. as well as infertility. Feeding difficulties usually resolve by the end of the first year of life, and between 1 and 6 years of age, patients develop marked hyperphagia and “foraging” behavior (foraging, building up hidden stores). This behavior and low metabolism cause severe obesity. Obesity is the leading cause of death, mainly due to cardiopulmonary disease and NIDDM (type II). If obesity can be effectively treated, life expectancy can be nearly normal.

Other phenotypes associated with the syndrome include poor sexual development in males, behavioral problems, and mental retardation. Many individuals with the syndrome go undiagnosed, so its frequency of occurrence is not known.

***Questions for control:***

1. explain principles of non-mendelian genetic disorders classification.
2. identify clinical features and manifestation of non-mendelian genetic disorders.
3. principles of diagnosis of non-mendelian genetic disorders and discuss related ethical and legal issues.
4. summarize principles of management of sex-linked (dominant and recessive) disorders (prevention, treatment) and discuss related ethical and legal issues.
5. principles of management of non-mendelian genetic disorders (prevention, treatment) and discuss related ethical and legal issues.
6. demonstrate respect for the patient's religious, cultural, social and ethical beliefs and understanding of how that might affect the decisions the patients make.
7. work with genetic databases (OMIM & etc).

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**Lecture 9-10**

***Fundamentals of population genetics***

***Goal:***

Demonstrate the understanding of population genetics, Hardy-Weinberg’s law, and the impact of different factors to the population.

***Content:***

Fundamentals of the Population Genetics.

Demographic characteristics.

Types of populations, marital structure of populations, genetic characteristics of the population.

Hardy-Weinberg’s law.

Hardy-Weinberg equilibrium.

Genetic burden of populations: concept and medical significance.

Impact of gene drift, mutation, migration, and natural selection on the population.

Bottle neck effect.

Founder effect.

It is the spreading and distribution of hereditary traits and genes which controlled it in different groups of people in certain areas.

The term population refers to the total number of individuals of a species occupying a particular geographic area at a given time. A species has many populations inhabiting different regions.

All genes separated info categories: having universal spreading, for example gene of infantile Amaurotic Idiocy (Tay-Sachs Disease) due to an error in fat metabolism, child brain and spinal cord are damaged, this results in mental retardation and paralysis. The child dies in 3 or 4 years. This is caused by recessive gene in homozygous condition 1% people of Europe affect by this gene;

Gene of red-green colorblindness is the inability of certain human beings to distinguish red from green colour. It is a sex-linked trait, and is preducted by a recessive gene, which present in 7% of males and 0,5 % females, but in heterozygous condition this gene present in 13% of females.

Genes spreading in certain regions, for example sickle anemia is a hereditary disease found widely in tropical Africa and also in American blacks whose ancestors came from that part of Africa. It is characterized by sickle-shaped (crescentic) red blood cells formed under low oxygen conditions. Change in the shape of red blood cells is due to the presence in them of a defective type of hemoglobin called hemoglobin S, gene of inborn dislocation of hip found in North-east of Russia.

Population-statistical method helps to study probability of individuals with certain genotypes in this population or relative marriages.

It helps to define the frequency of carriers in recesses of gene heterozygous condition.

***Questions for control:***

1. Characterize population and genetic processes: mutations, selection, migration, and gene drift.
2. Explain patterns of the distribution of genes that make up the gene pool, including genes that determine hereditary human diseases and make links with disease cases discussed earlier.
3. Know how to apply the Hardy-Weinberg equilibrium and solve problems concerning genotype and allele frequencies.
4. Interpret scenarios about factors responsible for genetic variation in/ among populations.
5. Justify the importance of studying hereditary diseases in human populations, its genetic diversity, identifying the frequencies of individual diseases and assessing the total load of hereditary human diseases.
6. Explain the phenomenon of a person's genetic burden and discuss hereditary diseases as part of a genetic burden.
7. Discuss the importance of determination of the burden of hereditary diseases in human populations, the study of the magnitude and structure of the burden of hereditary diseases to determine the amount of medical, social and rehabilitation assistance to the population.

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**Lecture 11-12**

***Polygenic multifactorial disorders***

***Goal:***

Demonstrate the understanding of polygenic multifactorial disorders, their clinical features and transmission.

***Content:***

Polygenic multifactorial disorders: characteristics, cause, mechanisms, frequency, phenotypic manifestation, clinical significance.

Diagnosis and management of polygenic diseases.

Epidemiology of polygenic diseases.

Diabetes mellitus: features and symptoms, classification, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

How Insulin works. The role of Glucose.

Prediabetes: causes and risk groups.

Differences between Diabetes 1 type and Diabetes 2 type. Complications.

Schizophrenia: features and symptoms, classification, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Family Hypercholesterolemia: features and symptoms, classification, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Arterial hypertension: features and symptoms, classification, causes, mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

There are two main types of diabetes mellitus: type I (insulin-dependent - IDDM) and type II (non-insulin-dependent - NIDDM), accounting for 10 and 88% of all cases, respectively. They differ in typical age of onset, concordance of identical twins, and association with specific alleles of the major histocompatibility complex (MHC). Familial accumulation is observed in both types of diabetes mellitus, but only type I or II is usually present in one family.

Type I diabetes mellitus occurs in the white population with a frequency of about 1 in 500 (0.2%), in African and Asian populations - less often. It is usually found in childhood or adolescence and is caused by autoimmune damage to the insulin-producing β cells of the pancreas. In the overwhelming majority of sick children, already in early childhood, long before the development of obvious manifestations of the disease, numerous autoantibodies against a number of endogenous proteins, including insulin, are produced.

***Questions for control:***

1. identify clinical features of polygenic multifactorial disorders and explain its clinical variability.
2. explain the mechanism of polygenic inheritance and summarize their role in clinical variability of polygenic disorders.
3. explain principles of diagnosis and genetic screening of polygenic disorders and discuss related ethical and legal issues.
4. explain principles of management of polygenic disorders (prevention, treatment) and discuss related ethical and legal issues.
5. explain risk assessment strategies for polygenic disorders.
6. discuss the impact of diagnosis of a genetic condition on the individual and the family.
7. demonstrate respect for a patient's religious, cultural, social and ethical beliefs and understand how that might affect the decisions the patients make.
8. work with genetic databases (OMIM & etc).

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**Lecture 13**

***Cancer Genetics and Genomics***

***Goal:***

Demonstrate the understanding of cancer genetics and genomics, hereditary cancer syndromes and familial occurrence of cancer.

***Content:***

Cancer Genetics and Genomics. Cancer genes.

Hereditary cancer syndromes.

Familial occurrence of cancer. Sporadic cancer and genetic bases.

Genetic technology in cancer prevention, diagnosis and therapy.

[Breast cancer](https://en.wikipedia.org/wiki/Breast_cancer): causes and genetic mechanism (clinical and genetic variants), diagnosis, management (prevention and treatment), prognosis, epidemiology.

Cancer. Growth and division of normal cells are regulated by control mechanisms. These control mechanisms result in fixed life span for cells and for the organisms. One such control mechanism is contact inhibition. As a result of multiplication, the cells become crowded and come in contact with one another. This surface contact checks movement and division of cells. Therefore, the genes which control these processes are turned off. Vertebrate cells grown in a culture adhere to the bottom as they need support, divide, and keep in contact with one another and spread as a monolayer. Cell to cell contact inhibits their growth. Cancer is a disease of cells wherein the control mechanism that normally restricts cell proliferation does not operate. In other words, in the case of cancer cells, the mechanism of contact inhibition does not function. The cells continue to divide, forming a tissue mass called tumour.The cancer cells may invade other tissues and cause tumours in them also. Cancer is caused, not only by viruses, but also by other mutagens such as radiation and chemicals. All these factors are called carcinogens.They alter (activate) the protooncogenes.Altered protooncogenes are called oncogenes.Alteration may in­volve breaking into fragments, amplification or shifting to a new chromosomal location. Intact genes control normal growth and development of cells. Alteration in genes leads to the formation of abnormal proteins, change in gene environment, suspension of the mechanism that controls cell division, which cause uncontrolled cell division and growth, and this is cancer.

***Questions for control:***

1. identify clinical features of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer) and explain its lifetime prevalence, genetic variability and summarize data on hereditary cancer syndromes and syndromes with familial cancer.
2. explain genetic mechanisms of oncogenesis on [breast cancer and](https://en.wikipedia.org/wiki/Breast_cancer) summarize their role in clinical variability of hereditary cancer syndromes and syndromes with familial cancer.
3. compare and contrast different diagnostic strategies of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer) and summarize principles of diagnosis of hereditary cancer syndromes and syndromes with familial cancer and discuss related ethical and legal issues.
4. compare and contrast different management strategies of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer) and summarize principles of management of hereditary cancer syndromes and syndromes with familial cancer (prevention, treatment) and discuss related ethical and legal issues.
5. summarize epidemiologic data of hereditary cancer syndromes and syndromes with familial cancer on the example of [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer).
6. discuss the impact of diagnosis of hereditary cancer syndromes and syndromes with familial cancer on the individual and the family.
7. demonstrate respect for a patient's religious, cultural, social and ethical beliefs and understand how that might affect the decisions the patients make.

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**Lecture 14-15**

***Polygenic disorders: developmental malformation***

***Goal:***

Demonstrate the understanding of developmental malformation, their causes and transmission.

***Content:***

Polygenic disorders: developmental malformation.

Teratogenesis

Classification, causes, mechanisms, prevalence, phenotypic manifestation, clinical significance.

Neural tube defects (NTDs): definition, types, causes, mechanisms, diagnosis, prevention, epidemiology and management.

Cleft lip and cleft palate: definition, types, causes, mechanisms, diagnosis, prevention, epidemiology and management.

Hip dysplasia: definition, types, causes, mechanisms, diagnosis, prevention, epidemiology and management.

Neural tube defects (e.g., spina bifida and anencephaly) may be diagnosed prenatally by detecting high alpha-fetoprotein levels in the amniotic fluid or in the maternal serum.

Spina bifida usually occurs in the sacrolumbar region. Includes the following variations:

- spina bifida occulta is defect in the ventral arches, occurs in 10% of the population;

- spina bifida with meningocele occurs when the meninges project through a vertebral defect, forming a sac filled with CSF;

- spina bifida with meningomyelocele occurs when the meninges and spinal cord project through a vertebral defect, forming a sac;

- spina bifida with myeloschisis results in an open neural tube that lies on the surface of the back.

***Questions for control:***

1. identify clinical features of developmental malformations and explain their clinical variability.
2. explain principles of diagnosis of developmental malformation in general and discuss related ethical and legal issues.
3. explain management of developmental malformation in general (prevention, treatment) and  discuss related ethical and legal issues.
4. discuss the impact of diagnosis of developmental malformation on the individual and the family.
5. demonstrate respect for a patient's religious, cultural, social and ethical beliefs and understand how that might affect the decisions the patients make.
6. work with genetic databases (OMIM & etc).

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