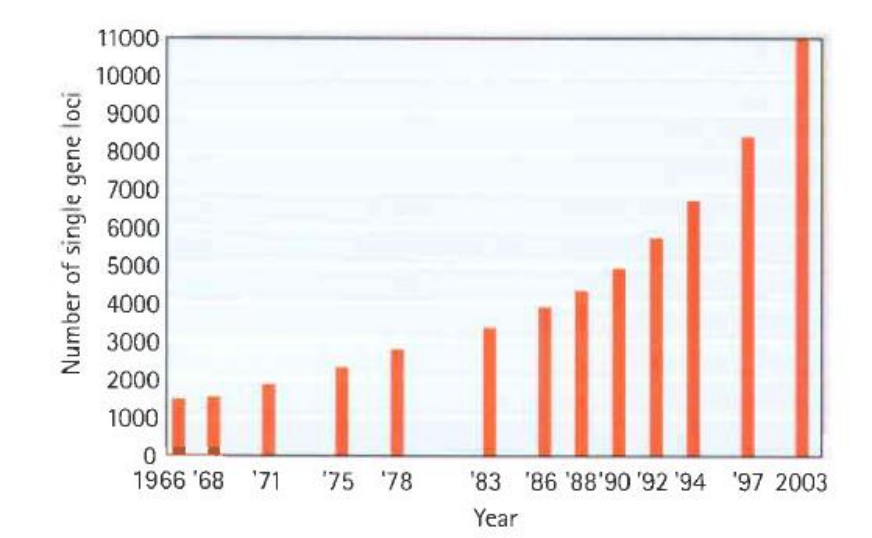
Lecture 11.
Human genetic diseases

Lovinskaya Anna Vladimirovna,

PhD, Departure of Molecular Biology and Genetics

Hereditary conditions:

- Single gene disorders (albinism);
- Chromosome abnormalities (Down syndrome);
- Multifactorial disorders (diabetes mellitus);
- Acquired somatic genetic disease (cancer)



Histogram showing the rapid increase in recognition of conditions and characteristics (traits) showing single-gene inheritance (Adapted from McKusick 1998 and OMIM)

The impact of genetic factors in disease at different ages

Spontaneous miscarriages. A chromosome abnormality is present in 40-50% of all recognized first-trimester pregnancy loss. Approximately 1 in 6 of all pregnancies results in spontaneous miscarriage, thus around 5-7% of all recognized conceptions are chromosomally abnormal.

Newborn infants. Of all neonates, 2-3% have at least one major congenital abnormality, of which at least 50% are caused exclusively or partially by genetic factors. The incidences of chromosome abnormalities and single-gene disorders in neonates are approximately 1 in 200 and 1 in 100, respectively.

Childhood. Genetic disorders account for 50% of all childhood blindness, 50% of all childhood deafness and 50% of all cases of severe learning difficulty. In developed countries genetic disorders and congenital malformations together also account for 30% of all childhood hospital admissions and 40-50% of all childhood deaths.

Adult life. Approximately 1% of all malignancy is caused by single-gene inheritance, and between 5% and 10% of common cancers (breast, colon and ovary) have a strong hereditary component. By the age of 25 years, 5% of the population will have a disorder in which genetic factors play an important role.

INBORN ERRORS IN METABOLISM

In excess of 200 inborn errors of metabolism are known which can be grouped by either the ***metabolite, metabolic pathway, function of the enzyme or cellular organelle*** involved. Most inborn errors of metabolism are inherited in an autosomal recessive or X-linked manner with only a few being inherited in an autosomal dominant manner. This is because the defective protein in most inborn errors is an enzyme which is diffusible, and there is usually sufficient residual activity in the heterozygous state (i.e. loss-of-function mutation) for the enzymic to function normally in most situations. If, however, the reaction catalysed by an enzyme is rate limiting (i.e. haploinsufficiency mutation) or the gene product is part of a multimeric complex (i.e. dominant-negative mutation), the disorder can manifest in the heterozygous state, i.e. be dominantly inherited.

Table 18.1 Classification of Inborn Errors of Metabolism

1 *Disorders of Amino Acid and Peptide Metabolism*
- 1.1 Urea cycle disorders & inherited hyperammonemias
- 1.2 Organic acidurias
- 1.3 Metabolism of branched-chain amino acids (not organic acidurias)
- 1.4 Phenylalanine or tyrosine metabolism
- 1.5 Metabolism of sulfur amino acids
- 1.6 Histidine, tryptophan or lysine metabolism
- 1.7 Serine, glycine or glycerate metabolism
- 1.8 Ornithine or proline metabolism
- 1.9 Amino acid transport
- 1.10 Amino acid metabolism
- 1.11 Gamma-glutamyl cycle
- 1.12 Other peptide metabolism

2 *Disorders of Carbohydrate Metabolism*
- 2.1 Galactose metabolism
- 2.2 Fructose metabolism
- 2.3 Pentose metabolism
- 2.4 Glycerol metabolism
- 2.5 Glyoxylate metabolism
- 2.6 Glucose transport
- 2.7 Gluconeogenesis
- 2.8 Glycogen storage disorders

3 *Disorders of Fatty Acid and Ketone Body Metabolism*
- 3.1 Lipolysis
- 3.2 Carnitine transport & the carnitine cycle
- 3.3 Mitochondrial fatty acid oxidation
- 3.4 Ketone body metabolism
- 3.5 Other fatty acid & ketone body metabolism

4 *Disorders of Energy Metabolism*
- 4.1 Pyruvate metabolism
- 4.2 Citric acid cycle
- 4.3 Mitochondrial respiratory chain
- 4.4 Mitochondrial membrane transport
- 4.5 Unspecified mitochondrial disorders
- 4.6 Creatine metabolism
- 4.7 Other energy metabolism

5 *Disorders in the Metabolism of Purines, Pyrimidines, and Nucleotides*
- 5.1 Purine metabolism
- 5.2 Pyrimidine metabolism
- 5.3 Nucleotide metabolism

6 *Disorders of the Metabolism of Sterols*
- 6.1 Sterol biosynthesis
- 6.2 Bile acid biosynthesis
- 6.3 Bile acid metabolism & transport
- 6.4 Other metabolism of sterols

7 *Disorders of Porphyrin and Heme Metabolism*

8 *Disorders of Lipid and Lipoprotein Metabolism*
- 8.1 Inherited hypercholesterolemias
- 8.2 Inherited hypertriglyceridemias
- 8.3 Inherited mixed hyperlipidemias
- 8.4 High density lipoprotein metabolism
- 8.5 Inherited hypolipidemias
- 8.6 Other lipid & lipoprotein metabolism
- 8.7 Unspecified disorders of lipid & lipoprotein metabolism

9 *Congenital Disorders of Glycosylation and Other Disorders of Protein Modification*
- 9.1 Protein N-glycosylation
- 9.2 Protein O-glycosylation
- 9.3 Glycosphingolipid & glycosylphosphatidylinositol anchor glycosylation
- 9.4 Multiple glycosylation & other glycosylation pathways
- 9.5 Protein ubiquitinylation

10 *Lysosomal Disorders*
- 10.1 Mucopolysaccharidoses
- 10.2 Oligosaccharidoses
- 10.3 Sphingolipidoses
- 10.4 Ceroid lipofuscinoses, neuronal (CLN)
- 10.5 Lysosomal export disorders
- 10.6 Other lysosomal disorders

11 *Peroxisomal Disorders*
- 11.1 Peroxisome biogenesis
- 11.2 Rhizomelic chondrodysplasia punctata
- 11.3 Peroxisomal alpha-, beta-, & omega-oxidation
- 11.4 Other peroxisomal disorders

12 *Disorders of Neurotransmitter Metabolism*
- 12.1 Metabolism of biogenic amines
- 12.2 Metabolism of gamma-aminobutyrate

13 *Disorders in the Metabolism of Vitamins and (Non-Protein) Cofactors*
- 13.1 Folate metabolism & transport
- 13.2 Cobalamin absorption, transport & metabolism
- 13.3 Pterin metabolism
- 13.4 Vitamin D metabolism & transport
- 13.5 Biotin metabolism
- 13.6 Pyridoxine metabolism
- 13.7 Thiamine metabolism
- 13.8 Molybdenum cofactor metabolism
- 13.9 Other vitamins & cofactors

14 *Disorders in the Metabolism of Trace Elements and Metals*
- 14.1 Copper metabolism
- 14.2 Iron metabolism
- 14.3 Zinc metabolism
- 14.4 Phosphate, calcium & vitamin D metabolism
- 14.5 Magnesium metabolism
- 14.6 Other trace elements and metals

15 *Disorders and Variants in the Metabolism of Xenobiotics*
- 15.1 Cytochrome P450-mediated oxidation
- 15.2 Other enzymes that oxidise xenobiotics
- 15.3 Xenobiotics conjugation
- 15.4 Xenobiotics transport

Adapted from Society for the Study of IEMs, 2011.

HUMAN IMMUNODEFICIENCY SYNDROMES

Although many inherited immunodeficiency diseases have now been identified, the first immunodeficiency disease was not described until 1952. Most of the gene defects that cause these inherited immunodeficiencies are recessive and, for this reason, many of the known immunodeficiencies are caused by mutations in genes on the X chromosome. Immunodeficiency diseases that affect various steps in B- and T-lymphocyte development have been described, as have defects in surface molecules that are important for T- or B-cell function. Defects in phagocytic cells, in complement, in cytokines, in cytokine receptors, and in molecules that mediate effector responses also occur. Thus, immunodeficiency can be caused by defects in either the adaptive or the innate immune system.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	ADA deficiency	No T or B cells	General
	PNP deficiency	No T or B cells	General
	X-linked *scid*, γ_c chain deficiency	No T cells	General
	Autosomal *scid* DNA repair defect	No T or B cells	General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T and B cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott–Aldrich syndrome	X-linked; defective WASP gene	Defective anti-polysaccharide antibody and impaired T cell activation responses	Encapsulated extracellular bacteria
X-linked agamma-globulinemia	Loss of Btk tyrosine kinase	No B cells	Extracellular bacteria, viruses
X-linked hyper-IgM syndrome	Defective CD40 ligand	No isotype switching	Extracellular bacteria *Pneumocystis carinii* *Cryptosporidium parvum*
Common variable immunodeficiency	Unknown; MHC-linked	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
Natural killer (NK) cell defect	Unknown	Loss of NK function	Herpes viruses
X-linked lympho-proliferative syndrome	SH2D1A mutant	Inability to control B cell growth	EBV-driven B cell tumors
Ataxia telangiectasia	Gene with PI 3-kinase homology	T cells reduced	Respiratory infections
Bloom's syndrome	Defective DNA helicase	T cells reduced Reduced antibody levels	Respiratory infections

POLYGENIC AND MULTIFACTORIAL INHERITANCE

Multifactorial disorders

Congenital malformations:

- Cleft lip/palate;
- Congenital dislocation of the hip;
- Congenital heart defects;
- Neural tube defects;
- Pyloric stenosis;
- Talipes.

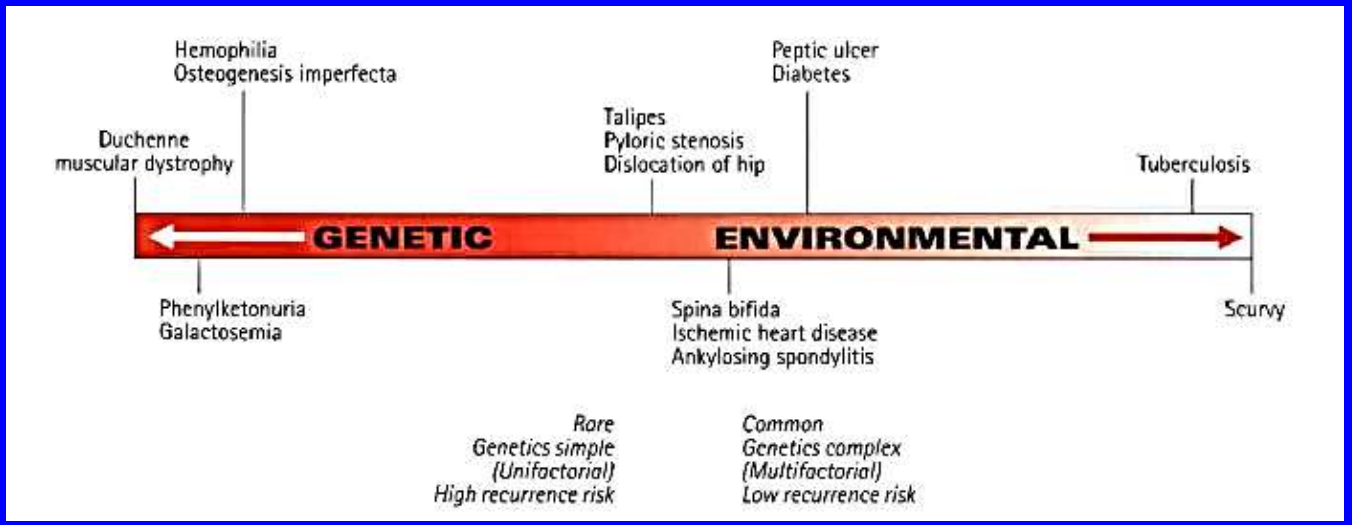
Acquired disease of childhood and adult life:

- Asthma;
- Autism;
- Diabetes mellitus;
- Epilepsy;
- Glaucoma;
- Hypertension;
- Inflammatory bowel disease (Crohn disease and ulcerative colitis);
- Ischaemic heart disease;
- Ischaemic stroke;
- Manic depression;
- Multiple sclerosis;
- Parkinson disease;
- Rheumatoid artritis;
- Schizophrenia

Many disorders demonstrate familial clustering that does not conform to any recognized pattern of Mendelian inheritance. Examples include several of the most common congenital malformations and many of the common acquired diseases of childhood and adult life. These conditions show a definite familial tendency but the incidence in close relatives of affected individuals is usually around 24%, instead of the much higher values that would be seen if these conditions were caused by mutations in single genes. As it is likely that many factors, both genetic and environmental, are involved in causing these disorders, they are generally referred to as showing ***multifactorial inheritance***.

The common diseases do not usually show a simple pattern of inheritance Instead, the contributing genetic factors are often multiple, interacting with one another and environmental factors in a complex manner. In fact, it is uncommon for either genetic or environmental factors to be entirely responsible for a particular common disorder or disease in a single individual In most instances both genetic and environmental factors are contributory, although sometimes one can appear more important than the other.

The common diseases and disorders such as diabetes mellitus, hypertension, cerebrovascular and coronary artery, disease, schizophrenia, the common cancers, and certain congenital abnormalities, in which both genetic and environmental factors are involved.



Human disease represented as being on a spectrum ranging from those that are largely environmental in causation to those that are entirely genetic.

Congenital abnormalities and dysmorphic syndromes

The formation of a human being, a process known as ***morphogenesis***, involves an extremely complicated and as yet incompletely understood interaction of genetic and environmental factors. Given the extraordinary complexity of this process it is not surprising that on occasion it goes wrong.

Approximately 2400 dysmorphic syndromes are described that are believed to be due to molecular pathology in single genes, and for about 500 the genes have been identified and a further 200 or more mapped. A further 500 or so sporadically occurring syndromes are recognized, for which the precise cause remains elusive.

Table 16.1 Examples of Major Congenital Structural Abnormalities

System and Abnormality	Incidence per 1000 Births
Cardiovascular	*10*
Ventricular septal defect	2.5
Atrial septal defect	1
Patent ductus arteriosus	1
Tetralogy of Fallot	1
Central Nervous System	*10*
Anencephaly	1
Hydrocephaly	1
Microcephaly	1
Lumbosacral spina bifida	2
Gastrointestinal	*4*
Cleft lip/palate	1.5
Diaphragmatic hernia	0.5
Esophageal atresia	0.3
Imperforate anus	0.2
Limb	*2*
Transverse amputation	0.2
Urogenital	*4*
Bilateral renal agenesis	2
Polycystic kidneys (infantile)	0.02
Bladder exstrophy	0.03

Box 16.1 Examples of Minor Congenital Structural Abnormalities

Preauricular pit or tag
Epicanthic folds
Lacrimal duct stenosis
Brushfield spots in the iris
Lip pits
Single palmar crease
Fifth finger clinodactyly
Syndactyly between second and third toes
Supernumerary nipple
Umbilical hernia
Hydrocele
Sacral pit or dimple

Table 16.2 Incidence of Structural Abnormalities

Incidence	(%)
Spontaneous Miscarriages	
First trimester	80–85
Second trimester	25
All Babies	
Major abnormality apparent at birth	2–3
Major abnormality apparent later	2
Minor abnormality	10
Death in perinatal period	25
Death in first year of life	25
Death at 1–9 years	20
Death at 10–14 years	7.5

GENETIC CAUSES OF MALFORMATIONS

Chromosome Abnormalities account for approximately 6% of all recognized congenital abnormalities, or possibly more if microarray-CGH positive cases are included. As a general rule, any perceptible degree of autosomal imbalance, such as duplication, deletion, trisomy, or monosomy, will result in severe structural and developmental abnormality, which may lead to early miscarriage.

Single-Gene Defects account for up to 10% of all congenital abnormalities. Some of these are isolated – i.e., they involve only one organ or system. Other single-gene defects result in multiple congenital abnormality syndromes involving many organs or systems that do not have any obvious underlying embryological relationship. Different mutations, allelic or non-allelic, can cause similar or identical malformations.

Table 16.3 Causes of Congenital Abnormalities

Cause	%
Genetic	*30–40*
Chromosomal	6
Single gene	7.5
Multifactorial	20–30
Environmental	*5–10*
Drugs and chemicals	2
Infections	2
Maternal illness	2
Physical agents	1
Unknown	50
Total	100

Table 16.4 Congenital Abnormalities That Can Be Caused by Single-Gene Defects

	Inheritance	Abnormalities
Isolated		
CENTRAL NERVOUS SYSTEM		
Hydrocephalus	XR	
Megalencephaly	AD	
Microcephaly	AD/AR	
OCULAR		
Aniridia	AD	
Cataracts	AD/AR	
Microphthalmia	AD/AR	
LIMB		
Brachydactyly	AD	
Ectrodactyly	AD/AR	
Polydactyly	AD	
OTHER		
Infantile polycystic kidneys	AR	
Syndromes		
Apert	AD	Craniosynostosis, syndactyly
EEC	AD	Ectodermal dysplasia, ectrodactyly, cleft lip/palate
Meckel	AR	Encephalocele, polydactyly, polycystic kidneys
Roberts	AR	Cleft lip/palate, phocomelia
Van der Woude	AD	Cleft lip/palate, lip pits

AD, Autosomal dominant; *AR*, autosomal recessive; *XR*, X-linked recessive.

GENETIC CAUSES OF MALFORMATIONS

Multifactorial Inheritance accounts for the majority of congenital abnormalities in which genetic factors can clearly be implicated. These include most isolated ('non-syndromal') malformations involving the heart, central nervous system, and kidneys (Box 16.2).

Genetic Heterogeneity is means that specific congenital malformations can have many different causes, hence the importance of trying to distinguish between syndromal and isolated cases. This causal diversity has become increasingly apparent as developments in molecular biology have led to the identification of highly conserved families of genes that play crucial roles in early embryogenesis.

Box 16.2 Isolated (Non-Syndromal) Malformations that Show Multifactorial Inheritance

Cardiac
- Atrial septal defect
- Tetralogy of Fallot
- Patent ductus arteriosus
- Ventricular septal defect

Central Nervous System
- Anencephaly
- Encephalocele
- Spina bifida

Genitourinary
- Hypospadias
- Renal agenesis
- Renal dysgenesis

Other
- Cleft lip/palate
- Congenital dislocation of hips
- Talipes

ENVIRONMENTAL AGENTS (TERATOGENS)

An agent that can cause a birth defect by interfering with normal embryonic or fetal development is known as a ***teratogen***. Many teratogens have been identified and exhaustive tests are now undertaken before any new drug is approved for use by pregnant women. The potential effects of any particular teratogen usually depend on the dosage and timing of administration during pregnancy, along with the susceptibility of both the mother and fetus.

Table 16.6 Drugs With a Proven Teratogenic Effect in Humans

Drug	Effects
ACE inhibitors	Renal dysplasia
Alcohol	Cardiac defects, microcephaly, characteristic facies
Chloroquine	Chorioretinitis, deafness
Diethylstilbestrol	Uterine malformations, vaginal adenocarcinoma
Lithium	Cardiac defects (Ebstein anomaly)
Phenytoin	Cardiac defects, cleft palate, digital hypoplasia
Retinoids	Ear and eye defects, hydrocephalus
Streptomycin	Deafness
Tetracycline	Dental enamel hypoplasia
Thalidomide	Phocomelia, cardiac and ear abnormalities
Valproic acid	Neural tube defects, clefting, limb defects, characteristic facies
Warfarin	Nasal hypoplasia, stippled epiphyses

ACE, Angiotensin-converting enzyme.

Table 16.7 Infectious Teratogenic Agents

Infection	Effects
Viral	
Cytomegalovirus	Chorioretinitis, deafness, microcephaly
Herpes simplex	Microcephaly, microphthalmia
Rubella	Microcephaly, cataracts, retinitis, cardiac defects
Varicella zoster	Microcephaly, chorioretinitis, skin defects
Bacterial	
Syphilis	Hydrocephalus, osteitis, rhinitis
Parasitic	
Toxoplasmosis	Hydrocephalus, microcephaly, cataracts, chorioretinitis, deafness

Thank you for attention!