

Criteria necessary for accreditation of the subject “Human Genetics”

- 1) Mandatory classes:
 - Lecture “Clinical Human Genetics”, Mon. 8:30-9:15am, 6th semester
- 2) Concordant class
 - Exercises for “Human Genetics”, Mon. 9:15-10:00 am, 6th semester
- 3) Record of achievement:
 - Multiple Choice Exam at the end of the 6th semester
 - By completing questions in WueCampus, a total of four bonus points can be received towards the exam
- 4) Learning objective:
 - The content and accreditation of “Human Genetics” follows the catalog for the subject of “Human Genetics” (§27 Section 1 Clause 4 ÄAppO)

1.Fundamentals for “Human Genetics”

1.1 Historical development

1.1.1 The validity of Mendel’s laws even in humans (discovery of blood types etc.)

1.1.2 Eugenics as one of the main ideas in Human genetics in the first half of the 20th century; examples why eugenics does not work (new mutations, recessive mutations in healthy etc.)

1.1.3 Hardy-Weinberg principle

1.1.4 Beginning of modern human genetics in 1959 with the discovery of the chromosomal basis of the Down Syndrome; establishing DNA sequence analytics in the 1970s and 1980s; Human Genome Project (1990-2001), Array and Next Generation Sequencing technologies

1.2 Cytogenetic and molecular basis

1.2.1 Mitosis and Meiosis; Differences between male and female meiosis as the foundation for paternal and maternal age effects

1.2.2 Paternal effects for dominant mutations; Examples for monogenic (Achondroplasia, craniosynostosis) and multifactorial diseases, which often arise through new mutations

1.2.3 Maternal effects for the development of chromosomal illnesses, especially Trisomy 21

1.2.4 Structure, genetic content, function and evolution of the gender chromosomes

1.2.5 Structure (5’UTR, promotor, exon, intron, 3’UTR) and regulation (splicing, processing of mRNA) of mammals; gene variants and mutations (germ line vs. somatical)

1.2.6 Structure (genes, repetitive DNA-elements etc.), variability and evolution of the human genome

1.3 Important terms and tools

1.3.1 Syndrome: Definition, number and frequency of human genetic diseases

- 1.3.2 Databank (OMIM, Orphanet, etc.)
- 1.3.3 Genetic consults (Indications, procedures, aspects and consequences)
- 1.3.4 Family tree analysis and symbols
- 1.3.5 Risk calculation in monogenic and multifactorial illnesses; risk of repetition
- 1.3.6 Genetic diagnostics (cytogenetic and molecular analysis methods, mutation types, genetic heterogeneity, laws concerning genetic diagnostics, etc.

2. Monogenic diseases

2.1 Autosomal dominant inheritance

- 2.1.1 Heredity process, family tree characteristics, risk of repetition in various family constellations
- 2.1.2 New mutations; selfish spermatogonial selection (examples FGFR3 mutations in achondroplasia)
- 2.1.3 Germ cell mosaicism (i.e. Neurofibromatosis Type 1), emergence and consequences
- 2.1.4 Reduced penetrance (i.e. in hereditary oncologic diseases) and variable expressivity (i.e. in NF1, tuberous sclerosis)
- 2.1.5 Chorea Huntington as an example for a disease with late manifestation: Pathogenesis (Trinucleotide-repeat-Expansion in the protein coding part of a gene, course of the illness, diagnostic versus predictive gene testing, anticipation through repeat lengthening in the male germ line)
- 2.1.6 Myotonic Dystrophy as an example of a RNA- illness: Trinucleotide repeat expansion in the non-protein coding section (3'UTR) of a gene, affected organ systems (multisystem disorders), congenital and late manifesting forms, anticipation through repeat lengthening in the female germ line
- 2.1.7 Osteogenesis imperfecta; clinical and molecular classification, mutation with a dominant-negative effect (grave course) versus haploinsufficiency (mild course)
- 2.1.8 Marfan Syndrome, clinical characteristics and pathogenesis

2.2 Autosomal-recessive inheritance

- 2.2.1 Heredity process, family tree characteristics
- 2.2.2 Calculation of heterogenic frequency in the population (with knowledge of the frequency of a disease); calculation of risk of repetition in various constellations
- 2.2.3 Blood-relationship of parents as a risk for autosomal-recessive and multifactorial disorders
- 2.2.4 Different frequencies of autosomal-recessive disorders in various populations, especially ethnically isolated populations with Founder-Effect (Tay-Sachs Disease)
- 2.2.5 Heterocytotic advantage (i.e. in Thalassemia)

2.3 X-chromosomal inheritance

2.3.1 Mechanism and functional consequences of X-inactivation (women as x-chromosomal mosaics); significance

2.3.2 Heredity process in X-chromosomal recessive inheritance, family-tree characteristics, calculation of risk of repetition in various constellations

2.3.3 Frequent new mutations and germ cell mosaicism

2.3.4 Hemophilia A and B: molecular pathogenesis, clinical presentation and treatment

2.3.5 Duchenne and Becker Muscle dystrophy: Pathomechanism (intragenic deletions and duplications with or without frameshift), clinical course

2.3.6 X-chromosomal-dominant inheritance in Rett-syndrome and Phosphate diabetes

2.4 Mitochondrial inheritance

2.4.1 Comparison of nuclear genome (>22000 genes) and mitochondrial genome (37 genes)

2.4.2 Respiratory chain function of mitochondrial genes

2.4.3 Heteroplasmy and other characteristics in the mitochondrial inheritance

2.4.4 Leber's Optic atrophy and other diseases with mitochondrial inheritance

2.4.5 Nucleus encoded mitochondrial disorders

2.5 Metabolic diseases

2.5.1 Definition, heredity, characteristics, and population-specific frequencies

2.5.2 Classification, inheritance, characteristics, population-based frequencies

2.5.3 Alkaptonuria – important historical example

2.5.4 Phenylketonuria as an example for a treatable metabolic illness, significance for newborn screenings

2.5.5 Biochemical screenings; newborn screening in Germany and its advancement

2.5.6 Enzyme replacement therapy (i.e. in Mucopolysaccharidosis)

2.5.7 Hemochromatosis, lactose-intolerance, familial hypercholesterolemia as another example for important metabolic diseases

2.5.8 In-depth carrier testing for autosomal-recessive inheritance before pregnancy (pros and cons)

2.5.9 Basics to pharmacogenetics; cytochrome variants, cholinesterase defects

2.6 Syndromal and non-syndromal mental handicap

2.6.1 Classification of intellectual disabilities, intelligence tests

2.6.2 Frequencies gender distribution of mental deficiencies

2.6.3 Model of defective brain development; Connection between cognition, motor skills, behavior, and anatomic structural anomalies

2.6.4 Different inheritance: William-Beuren syndrome (autosomal-dominant) Smith-Lemli-Opitz- syndrome (autosomal-recessive), Fragile x-syndrome (gender bound), MELAS-syndrome (mitochondrial)

2.6.5 Dysmorphia in syndromology on the basis of examples, examination, utilization of Syndrome search programs such as Possum

2.6.7 Trinucleotide Repeat Disorders and Fragile X-Syndrome: Pathomechanism (expansion 5'UTR), permutation (repeat expansion in the female germ line, FXTAS), clinical manifestation caused by expanded alleles in both sexes

2.6.8contiguous gene syndrome and Williams Syndrome

3. Multifactorial illnesses

3.1 Foundation for multifactorial inheritance

3.1.1 Quantitative features (i.e. intelligence and body size) and qualitative features (i.e. congenital malformation); threshold model

3.1.2 empirical rates of risk, risk of repetition in first- and second- degree relatives, correlation between risk of repetition and degree of relative, number and under spec. circumstances gender of the family members, as well as the degree of severity of their illness

3.1.3 Impact of various genes and environmental factors

3.1.4 Tools for the identification of risk gene variations: twin studies, familial aggregation, (genome-wide) association studies

3.2 Congenital multifactorial disorders

3.2.1 Neural tube defect: evolutionary origin, various manifestations (Spina bifida, Meningomyelocele , Anencephalus), Folic acid prophylaxis during pregnancy, risk of repetition, prenatal diagnostics

3.2.2 Cheilognathopalatoschisis

3.2.3 Carter effect in Pyloric stenosis (male gender more frequently affected) and congenital hip dysplasia (female predominance)

3.3 Multifactorial illnesses in adults (complex disorders)

3.3.1 Cardiovascular, metabolic and psychiatric diseases; in comparison to othe multifactorial disorders, high risk of repetition in those with one parent suffering from schizophrenia

3.3.1 Alzheimer: monogenic induced early- or late- manifesting multifactorial forms, staging and diagnostics; APOE4 as a risk gene variant for the late manifesting form; empirical risk rates

3.3.3 Infectious diseases: Dependence of HIV risk of infection on the quantity of CCR5 receptors and CCL3L1 gene copies

3.3.4 Protective and predisposing gene variants selected through evolution and general living condition and are therefore population dependent

4. Interference of the embryonic evolution and teratogenesis

4.1 Early embryonic development

- 4.1.1 Development of twins or multiples in humans; Difference between monozygotic and dizygotic twin pregnancies; anatomical differences and risks
- 4.1.2 Axis formation and early organogenesis in humans; basic principals of the cellulaf mechanism (induction, migration, diffusion, apoptosis)
- 4.1.3 Gastrulation and germ layer formation, teratoma formation
- 4.1.3 Extremity development and its disturbance (Phocomelia –Syndrome)

4.2 Teratogenesis

- 4.2.1 Birth defects give information about the chronological sequence of the embryotic development and its significance for teratogenesis
- 4.2.2 Deformations and disruptions
- 4.2.3 Known teratogens: maternal malnutrition, viral and bacterial noxae, important medication and substances that have teratogen effects

5. Chromosomal dysfunction

- 5.1.1 Chromosomal structure and function
- 5.1.2 Tissue suitable for chromosomal analysis; methods for chromosomal preparation, banding approach, karyotype interpretation, ISCN vocabulary
- 5.1.3 Aneuploidy and their formation; nondisjunction in meiosis; maternal post-zygotic mosaics
- 5.1.4 Structural aberrations

5.2 Autosomal aneuploidy

- 5.2.1 Possible causes for Down Syndrome: Free trisomy 21, mosaics, translocation trisomy
- 5.2.2 Developmental dysfunction in Down Syndrome; Dysmorphia, internal malformations, therapeutic measures, impact of early support, learning initiatives and self help groups, better life expectancy, high risk of Alzheimer as an adult, etc.
- 5.2.3 Trisomy 13 an 18: Development, clinical manifestation and prognosis

5.3 Sex chromosomal Aneuploidy

- 5.3.1 Turner-Syndrome: Monosomy X (oftentimes the paternal chromosome is missing, no age effect), mosaics, structural aberrations
- 5.3.2 Clinical characteristics of Turner Syndrome: primordial dwarfism (treatment with growth hormones), primary amenorrhea (treatment with female sex hormone, infertility)
- 5.3.3 Miscarriage of most Monosomy X pregnancies
- 5.3.4 Klinefelter´s syndrome: clinical characteristics, therapy with male sex hormones; possible utilization of assisted reproduction procedures such as TESE and ICSI, breast cancer risk
- 5.3.5 XXX- women and XXY-men

5.4 Structural aberrations

- 5.4.1 Robertsonian and reciprocal translocation, inversions and deletions

5.4.2 Possible consequences of balanced paternal rearrangements: fertility problems, miscarriages, descendants with unbalanced karyotypes

5.4.3 Cytogenetically visible micro deletions: partial monosomy 5p (Cri-du-chat syndrome) and monosomy 4p (Wolf-Hirschhorn Syndrome)

5.5 Molecular cytogenetics

5.5.1 Fluorescent in situ hybridization as proof for micro deletions, FISH quick test, molecular karyotype analysis with array CGH (Comparative Genomic Hybridization) and SNP-arrays

5.5.2 Cytogenetic cryptic micro deletions, i.e. DiGeorge- Syndrome, Williams-Beuren Syndrome, etc.

5.6 Miscarriages

5.6.1 Chromosomal dysfunctions as the main cause for spontaneous abortions during the first trimester, triploidy, Turner Syndrome, Trisomy 16, etc.

5.6.2 Genetic causes for multiple miscarriages; Sex chromosomal aberrations or balanced translocations in one of the parents; thrombophilia

6. Reproduction and prenatal medicine

6.1 Fertility problems

6.1.1 Genetic causes for male infertility: Chromosomal dysfunction (i.e. Klinefelter's), Deletion of the azoospermia factor, congenital aplasia of vas deferens due to specific mutations in the CFTR gene for cystic fibrosis

6.1.2 Genetic Causes for female infertility: Chromosomal dysfunction (i.e. Turner); premutation in FMR1 gene for fraX Syndrome cause premature ovarian insufficiency

6.2 Disorders of sexual development

6.2.1 Gonosomal (SRY) and autosomal sex determining genes

6.2.2 Monogenic syndromes with dysfunction in the gender determination (i.e. XX-men) and gender differentiation (i.e. testicular feminization and androgen insensitivity syndrome)

6.2.3 Criteria for gender determination (genetic, somatic, social and personal status)

6.3 Prenatal diagnostics

6.3.1 Indications: maternal age effect (for chromosomal illnesses), genetic disorder, maternal anxiety, etc.

6.3.2 Legal basis: Gene diagnostic act requires consultation both before doing prenatal diagnostics and for communication of the results; no prenatal diagnostic for late manifesting illnesses, law on conflicts during pregnancies regulates among other things abortions; §218 defines the requirements for impunity with abortion

6.3.3 Non-invasive procedures: First trimester screening (maternal age, maternal serum parameters, nuchal translucency screening), malformation

ultrasound, Next-generation sequencing of free fetal and maternal DNA from maternal blood samples

6.3.4 Invasive procedures: Chorionic villus sampling (10th-12th gestation week, risk of miscarriage 2-5%; especially for those with high risk for a sick child or miscarriage) and amniocentesis (16th gestation week, cells have to be cultured for 1-2 weeks, risk of miscarriage <0.5%; especially for patients with high pregnancy age and quicktest)

6.3.5 Prenatal diagnostic of chromosomal disorders (Trisomy 21), genetic disorders (i.e. spinal muscular atrophy and fraX) and multifactorial illnesses (i.e. neural tube defects and congenital heart defects)

6.4 Preimplantation genetic diagnostics

6.4.1 Procedure of preimplantation development in utero and in vitro; Preimplantation diagnostics only possible with assisted reproduction

6.4.2 Embryo protection law defines the beginning of human life (Karyogamy) and prohibits preimplantation genetic diagnostics in totipotent embryonic cells (blastomere biopsy)

6.4.3 In Germany diagnostics is allowed for non-totipotent trophoblast cells (trophectoderm biopsy) and polar body diagnostics (preconception analysis)

6.4.4 Meaningful (grave hereditary illness in the family) and non-meaningful (gender selection, aneuploidy screening) indications for preimplantation genetic diagnostics

7. Epigenetics

7.1 Fundamentals of epigenetic inheritance

7.1.1 Inheritance of information, that is not encoded in the DNA sequence, but in reversible biochemical DNA modifications (i.e. DNA-methylation) and in chromatin (histone modification); in contrast the Mendel laws are based on irreversible gene and chromosome mutations/modifications

7.1.2 Epigenetic genome reprogramming in the germ line and in the early embryo

7.1.3 Imprinting, paternal specific gene activity, gender conflict

7.1.4 Epigenetic gene regulation in development, differentiation and disease processes (one individual, 1 genome, 100 epigenomes)

7.2 Abnormal human pregnancies

7.2.1 Dermoid cysts and teratomas in digynic and parthenogenesis pregnancies with two female genomes

7.2.2 Complete hydatiform mole in diandric pregnancies with two male genomes

7.2.3 Different phenotypes in diandric (partial hydatiform mole) and digynic (multiple malformations) triploidies

7.3 Imprinting disorders

7.3.1 Formation mechanism: uniparental disomy

7.3.2 Silver-Russel Syndrome (SRS) in UPD7 or abnormal Hypomethylation of ICR1 on chromosome 11; phenotypical characteristics

7.3.3 Maternal and paternal UPD14

7.3.4 Prader-Willi Syndrome and Angelman Syndrome as reciprocal imprinting disorders on chromosome 15; molecular causes and phenotypical manifestations of the disorders

7.3.5 Beckwith-Wiedemann Syndrome (BWS) caused by different malfunctions of ICR1 or ICR2 on chromosome 11; phenotypical manifestations; BWS (gigantism) and SRS (dwarfism) due to reciprocal methylation defects of ICR1 on chromosome 11

7.4 Fetal Origins of Health and Disease (DOHAD), Barker Hypothesis

7.4.1 Unfavorable environment in the early development lead to persistent epigenetic changes, which coincide with a higher susceptibility for various (cardiovascular, metabolic, psychiatric) illnesses later in life

7.4.2 The agouti mouse model as an example for the effects of random positive and negative environmental factors on the early embryonic development

7.4.3 Epigenetic effects of assisted reproductive procedures

7.4.4 Epigenetic effects of maternofetal over eating (i.e. gestational diabetes and maternal obesity) or malnutrition (famines)

8. Cancer genetics

8.1 Definition: Oncogenes, tumor suppressor genes, fusion genes, mutation mechanisms, loss-of-function and gain-of-function mutations, exogenic cancer sequences

8.1.2 Activation of proto-oncogenes in leukemia (CML, AML, ALL); Pathomechanisms and specific treatment

8.1.3 Adenoma-carcinoma sequence in colon carcinomas: Polyp formation, β -Catenin dependent WNT- Signaling pathway, RAS- gene family, gene amplification, chromosomal instability, loss of imprinting

8.2. Hereditary tumor syndromes

8.2.1 Two-Hit model from Knudson using familial Retinoblastomas as an example, loss of heterozygosity, impact of tumor suppressor genes

8.2.2 Multiple Endocrine Neoplasia type 1: definition, symptoms, tumor spectrum, MEN-gene and diagnostics

8.2.3 Multiple Endocrine Neoplasia type 2: RET-gene, phenotypes of the clinical subtypes, genotype-phenotype correlation, clinical support for families

8.2.4 Hereditary breast- and ovarian cancer: Comparison of sporadic and familial breast cancer, causing genes (DNA-repair), tumor spectrum, inclusion criteria, risk factor analysis with software, possibilities of early cancer recognition, prophylactic surgeries, differential diagnosis Li-Fraumeni-Syndrome

8.2.5 Hereditary colon carcinoma, HNPCC/Lynch-Syndrome: clinical characteristics, tumor spectrum, pathomechanism with microsatellite

instability, loss of DNA-Mismatch repair proteins, tumor suppressor model, early tumor screenings, inclusion criteria, clinical evaluation

8.2.6 Familial adenoma polyposis: Clinical characteristics, APC- gene, tumor suppressor model, screenings, predictive testing in children, mild course, differential diagnosis MUTYH- associated polyposis

8.2.7 Fanconi Anemia: clinical characteristics, Fanconi- complex proteins

8.2.8 Gorlin-Goltz syndrome: clinical characteristics, PTCH1 gene, and clinical patient support