Beta Thalassemia

Beta thalassemia is an autosomal recessive disorder caused by the absence or reduction of beta-globin chain synthesis, resulting in microcytic hypochromic anemia, an abnormal peripheral blood smear with nucleated red blood cells, and reduced amounts of hemoglobin A. For clinical purposes, beta thalassemia is divided into thalassemia major, thalassemia intermedia, and thalassemia minor. Thalassemia major is characterized by ineffective erythropoiesis and extramedullary hematopoiesis and is transfusion dependent. Thalassemia major manifests within the first year of life. Individuals with thalassemia intermedia present with symptoms later and have milder anemia that only rarely requires transfusion. Thalassemia minor is asymptomatic.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (21-hydroxylase insufficiency) is an autosomal recessively inherited disease in case of which cortisol and aldosterone synthesis in adrenal glands is disturbed. The disease manifests clinically during neonatal age causing virilisation and life-threatening salt-loss syndrome. Virilisation in girls manifests as enlargement of clitoris; in severe cases it may be difficult to identify the neonate's sex. In boys the virilisation is not easily diagnosable, but in them the disease may manifest during the first weeks after birth as adrenal crisis, expressed as hyponatraemia, hyperkalaemia and metabolic acidosis.

The congenital adrenal hyperplasia is caused by mutations in the **CYP21A2** gene. The incidence of congenital adrenal hyperplasia is about 1 per 15,000 neonates.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis

Cystic Fibrosis – CF

Cystic fibrosis (CF) is an autosomal recessive, multisystem disease. CF is characterized by recurrent lung infections, malabsorption, malnutrition, and male infertility. Cystic fibrosis is caused by thick and sticky mucus due to disturbances of salt homeostasis in cells.

CF is caused by mutations in the **CFTR** gene encoding cystic fibrosis transmembrane conductance regulator protein. The CFTR protein functions as a chloride channel expressed on epithelial cell membranes and controls the regulation of other transport pathways.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for family members of CF patients
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

FGFR2 gene mutation analysis

Fibroblast growth factors (FGFs) are a family of growth factors involved in regulating a variety of processes, including angiogenesis and wound healing as well as embryo development. FGFs function is binding to FGF receptors (FGFRs) and activating different signaling pathways. Several mutations in**FGFR genes** have been found to be related to a number of skeletal disease syndromes. FGFR2 gene has been shown to affect several processes, disruption of which can result in a number of disorders.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Genetic counseling
3. Prenatal diagnosis

FGFR2 gene mutation analysis is indicated by fetal increased nuchal translucency in the first trimester and/or skeletal abnormalities detected during the first or second trimester.

FGFR3 gene mutation analysis

Fibroblast growth factors (FGFs) are a family of growth factors involved in regulating a variety of processes, including angiogenesis and wound healing as well as embryo development. FGFs function is binding to FGF receptors (FGFRs) and activating different signaling pathways. Several mutations in FGFR genes have been found to be related to a number of skeletal disease syndromes. **FGFR3 gene**has been shown to participate in the regulation of several processes, disruption of which can result in a number of disorders.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Genetic counseling
3. Prenatal diagnosis

FGFR3 gene mutation analysis is indicated by fetal increased nuchal translucency in the first trimester and/or skeletal abnormalities detected during the first or second trimester.

Hutterite Genetic Diseases

A number of autosomal recessive disorders have been described in the **Hutterite population**. Some diseases − for example Limb-girdle muscular dystrophy, Carnitine Palmitoyltransferase I deficiency, and Cystic fibrosis − are very common in the Hutterite population. Genetic testing facilitates early diagnosis and improves health care services for individuals and families with genetic disorders.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Estimation of reproductive risks
4. Genetic counseling

Male Factor Infertility

Infertility is a widespread medical problem, affecting the lives of 15–20% of couples, with **male factor infertility** (MFI) occurring in almost half of the cases. The unfavourable genetic background is thought to be the cause in 15–30% of male factor infertility cases. Main genetic causes of male infertility are numerical and structural chromosomal aberrations of sex (**Klinefelter syndrome** 47XXY) and autosomal chromosomes, meiotic defects, microdeletions in the region q11.21-23 of the **Y-chromosome**, mutations in the **CFTR gene** and genetically determined syndromes in which infertility is a symptom. The correct determination of the genetic basis of infertility is important for the further treatment of patients.

A clear advantage of performing the **MFI-APEX** (arrayed primer extension) **assay** with the addition of a quick determination of **Y-deletions** is the simultaneous testing for a number of known genetic causes of male infertility. This allows **confirmation/ exclusion of diagnosis** and provides insight into the causes of infertility that could be valuable in planning the treatment for the patient. Furthermore, MFI testing is strongly recommended before a couple undergoes **assisted reproduction** in order to prevent the possible inheritance of the genetic lesion to the next generation.

Indications for genetic testing:

1. Confirmation of suspected diagnosis
2. Reasons other than genetic have been ruled out (environment and lifestyle related reasons, medical reasons that include hormone imbalance, infections, varicocele)
3. Patient’s phenotype is indicative of a syndrome or condition associated with genetic male infertility (for example, small testicles and lower testosterone levels in case of Klinefelter syndrome)

Noonan Syndrome

Noonan syndrome is an autosomal dominantly inherited disease characterized by short stature, congenital heart defect and delayed mental development of varying degree. Patients with Noonan syndrome also have a characteristic appearance: short neck, cervical skin fold, low set ears, hypertelorism. Additionally lymphatic system dysplasia may occur, which is the basis of cystic hygroma and occipital fold enlargement in the fetus.

The incidence of Noonan syndrome is about 1:1000-2500. Noonan syndrome is genetically heterogeneous. In 50% of patients mutations occur in the PTPN11 gene. 10% of cases are associated with mutations in the SOS1 gene, 3% in the RAF1 gene and 1% in the KRAS gene.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Parental testing in case of a causative mutation has been identified in an affected individual
3. Genetic counseling
4. Prenatal diagnosis

Sickle Cell Disease

Sickle-cell disease (SCD), also known as sickle-cell anemia is characterized by tendency of haemoglobin molecules within red cells to polymerise and deform the red cell into a sickle shape resulting in **vaso-occlusive events** (VOE). VOE are associated with tissue ischemia and variable degrees of **hemolysis**, both of which contribute to multi-organ dysfunction. Acute and chronic bone pain is the most characteristic feature of SCD. Chronic hemolysis leads to anemia, jaundice, cholelithiasis, and delayed growth and sexual maturation. Individuals with severe hemolysis are predisposed to pulmonary artery hypertension, priapism, and leg ulcers.

Sickle cell disease is inherited in an autosomal recessive manner.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Skeletal Dysplasia

Skeletal malformations are caused by a number of different hereditary disorders and syndromes resulting from mutations with many genes. The most common syndromes associated with skeletal malformations are **achondroplasia**, **craniosynostosis**, **campomelic dysplasia**,**hypochondroplasia**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Testing for at-risk family members
3. Determination of disease prognosis
3. Genetic counseling
4. Prenatal diagnosis

Testing is indicated by fetal increased nuchal translucency in the first trimester and/or skeletal abnormalities detected during the first or second trimester.

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessively inherited multiple malformation syndrome due to an inborn error cholesterol synthesis – insufficiency of enzyme 7-dehydroxycholesterol reductase. The syndrome is characterized by intrauterine and also postnatal growth retardation, moderate to severe mental retardation, malformations in many organ systems (cardiovascular, urogenital, gastrointestinal and central nervous systems). The patients have a characteristic appearance: ptosis, polydactyly, syndactyly of the II and III toes on both feet.

The incidence of SLOS is 1:20,000-70,000. SLOS is associated with mutations in the **DHCR7 gene**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the lower motor neurons in the spinal cord and the brain stem nuclei. The weakness is almost always symmetric and progressive. Poor weight gain, pneumonia, sleeping problems, scoliosis, and joint contractures are common symptoms of SMA.

Spinal muscular atrophy is divided into five subtypes (**SMA 0, SMA I, SMA II, SMA III, SMA IV**), distinguished by the age of onset and maximum function attained.

SMA is inherited in an autosomal recessive manner. Disease incidence rate is 4-10 per 100,000 live births.

Indications for genetic testing:

1. Differential diagnostics
2. Carrier testing for at-risk relatives
3. Prenatal testing for known familial mutations
4. Genetic counseling

Syndromes related to increased Nuchal Translucency of fetus

The ultrasound finding of **increased nuchal translucency** (NT) from weeks 11 to 14 of gestation is most commonly associated with**chromosomal abnormalities**. However, even in the absence of chromosomal defects, increased NT has been associated with an increased risk for adverse pregnancy outcome, including fetal abnormalities and genetic syndromes.

The **test of syndromes associated with increased NT of the fetus** allows examination of the most common genetic changes that cause syndromes such as **Congenital adrenal hyperplasia** (21-hydroxylase insufficiency),**Noonan syndrome**, **Smith-Lemli-Opitz syndrome** and **Spinal muscular atrophy**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis

Testing is indicated by fetal increased NT (measurement 3 mm and more) during weeks 11-14 of gestation. Before genetic testing it is recommended to exclude fetal aneuploidy.

Venous Thrombosis

The annual incidence of venous thrombosis ranges from approximately 1 to 3 per 1000 people. Venous thrombosis events often occur when multiple risk factors, including genetic and environmental, are present simultaneously. Acquired risk factors of venous thrombosis are age, immobilization, surgery, trauma, malignancy, myeloproliferative disorders, obesity, pregnancy, postpartum period, hormone

replacement therapy or use of oral contraceptives. Genetic risk factors are related to a 30- to 80-fold higher risk for developing a thrombotic episode.

Indications for genetic testing:

1. Vein thrombosis before the age of 50
2. Recurrent vein thrombosis in family
3. Identified genetic variant for higher risk of venous thrombosis in family
   For women in addition to the above named:
4. Myocardial infarction in 50-year-old women who are smoking
5. Vein thrombosis in the period of taking oral contraceptives
6. The presence of pregnancy complications, for example multiple miscarriages, preeclampsia and stillbirth.

Exome Sequencing

Exome sequencing includes the sequencing of the protein **coding regions** and their flanking**intronic regions** in ~20,000 genes of the human genome. The coding region represents 1-2% of the human **genome** but contain approximately 85% of disease-causing mutations. Exome sequencing can be an efficient tool for clinicians to confirm patients' diagnosis of complicated conditions not covered by conventional testing approaches.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Diagnosis of patients with genetic disorders for which diagnostic panels are not available
3. Identification of novel genes responsible for diseases
4. Genetic counseling