Brugada Syndrome

Brugada syndrome, caused by an ion channelopathy, is characterized by ST-segment abnormalities in leads V_1-V_3 on ECG and an increased risk of sudden death in patients with structurally normal hearts. Brugada syndrome manifests predominantly during adulthood, in patients between ages 20 to 40.

Symptoms include ventricular arrhythmia, syncope, and cardiac arrest usually during sleep or rest. In some patients sudden cardiac death may occur without any sign of clinical symptoms. Brugada syndrome may overlap with conduction disease. Symptoms such as first-degree AV block, intraventricular conduction delay, right bundle branch block, and sick sinus syndrome could be included in a differential diagnosis.

The prevalence of Brugada syndrome is estimated to affect 5 in 10,000 people worldwide. Although Brugada syndrome affects both men and women, the condition is more prevalent among men.

Brugada syndrome is inherited in an autosomal dominant manner.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Risk assessment of at-risk relatives
3. Prenatal diagnosis for known familial mutation
4. Differential diagnosis of Brugada syndrome from other genetic heart conditions
5. Genetic counseling

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is characterized by **high LDL** (low density lipoprotein)**cholesterol** level that cause atherosclerotic plaque deposition in the coronary arteries, increasing the risk for early cardiovascular disease and stroke.

Deposition of cholesterol is also found in the tendons of the hands, elbows, knees and feet (xanthomas) and around the eyes (xanthelasmas).

Heterozygous FH is associated with heterozygous pathogenic variant in one of three genes – LDLR, APOB, PCSK9, and occurs at a frequency of about 1:500. **Homozygous FH** is much rarer, occurring in about 1:1,000,000 in general population. Homozygous FH results from biallelic mutations in one of the following genes: LDLR, LDLRAP1, APOB, PCSK9.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for known familial mutations
3. Genetic counseling

Long QT Syndrome

Long QT Syndrome (LQTS) is a rare hereditary disease that is characterized by a **prolonged QT-interval** on the electrocardiogram (ECG) due to delayed repolarization of the heart. Affected individuals have an increased risk for ventricular tachycardia with syncope or even sudden death due to ventricular fibrillation.

The estimated prevalence of **LQTS** is one in 2000. The clinical symptoms of LQTS are quite variable depending on the causative mutation, age, gender, environmental factors and therapeutic interventions. The age of onset is usually younger than 40 years of age, however, the condition can occur as early as in infancy. The diagnosis and risk assessment of LQTS is based on patient's clinical symptoms, including **ECG findings**, as well as family history. However, the diagnosis of LQTS can be challenging since around 2.5% of the healthy population have prolonged QT-interval while some of LQTS patients do not exhibit abnormal ECG findings. Therefore, genetic testing is a valuable component in the assessment of LQTS patients.

LQTS is caused by mutations in genes encoding for the subunits of various ion channels. To date, over 600 disease causing mutations have been recognized in at least 15 genes. It has been shown that mutations in known LQTS related genes can be detected in more than 75% of patients with clinical diagnosis. Most commonly the mutations are detected in **KCNQ1** (LQT1), **KCNH2** (LQT2) and **SCN5A** (LQT3) genes and account for about 95% of mutations in affected individuals. The disorder is inherited as an autosomal dominant trait, although a rare subtype with autosomal recessive inheritance has been reported (Jervell and Lange-Nielsen Syndrome).

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Distinguishing different forms of LQTS to direct appropriate therapies
3. Testing of family members of the affected individuals
4. Carrier status detection of known mutation
5. Genetic counseling

Marfan Syndrome and Related Disorders

Marfan syndrome is a systemic disorder of connective tissue with multiple organ systems involvement. The main manifestations include ocular, skeletal, and cardiovascular systems. The syndrome may also affect lungs, skin, and dural sac surrounding the spinal cord. Cardiovascular manifestations typically include dilatation of the aorta, mitral valve prolapse, and enlargement of the proximal pulmonary artery.

Marfan syndrome is inherited in an autosomal dominant manner, caused by mutations in the FBN1 gene. Mutations in the FBN1 gene have also been associated with **MASS syndrome** (myopia, mitral valve prolapse, borderline and non-progressive aortic enlargement, and nonspecific skin and skeletal features), **mitral valve prolapse syndrome**, **ectopia lentis syndrome**, **Shprintzen-Goldberg syndrome**, and **Loeys-Dietz syndrome**.

Marfan syndrome shares overlapping phenotypic features with other syndromes including **congenital contractural arachnodactyly** (CCA), familial thoracic aortic aneurysms and aortic dissection (**TAAD**),**Ehlers-Danlos syndrome** (EDS), and **homocystinuria**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Differential diagnostics between Marfan syndrome and genetically/ phenotypically related disorders
3. Predictive testing for at-risk asymptomatic family members
4. Prenatal diagnosis for known familial mutation
5. Genetic counseling

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

Statin-Induced Myopathy

Statins inhibit the synthesis of cholesterol and promote the production of low density lipoprotein (LDL)-binding receptors in the liver resulting in an unusually marked decrease in the level of LDL, and a modest increase in the level of high density lipoprotein (HDL) circulating in blood plasma. Therefore, statin drugs are the primary pharmacologic treatment for **hypercholesterolemia** and **coronary artery disease** worldwide.

Despite their demonstrated safety and efficacy, 25% to 50% of individuals with cardiovascular disease are nonadherent with statin medications after one year. Although there may be multiple contributing factors, many experts report that a contributor to statin nonadherence is associated with side effects, including skeletal muscle toxicity due to poor or compromised metabolism of statin drugs.

Statin-induced myopathy has been associated with SLCO1B1 gene variant NM_006446.4:c.521T>C (rs4149056). The risk of myopathy may be substantially increased in patients who take 80 mg of**simvastatin** daily, as well as in those who are also receiving certain other drugs.

Indications for genetic testing:

1. Risk assessment for developing statin-induced myopathy
2. Optimizing the statin dose

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.