LABOR RENNER

# Gene Test Catalog

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The Labor Renner was established in 2001 and has been approved by the Austrian Federal Ministry for Health as an institution licensed for predictive and pre-symptomatic genetic testing for medical reasons. External Quality Assessment (EQA) includes participation in proficiency testing schemes of the following institutions: Österreichische Gesellschaft für Qualitätssicherung und Standardisierung medizinisch-diagnostischer Untersuchungen (ÖQUASTA), Deutsche vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL), Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien e.V. (INSTAND), European Molecular Genetics Quality Network (EMQN).

Dr. Renner is a member of the Society for Good Analytical and Laboratory Practice (Gesellschaft für Gute Analysen- und Laborpraxis, GALP), the Austrian Society for Human Genetics (Österreichische Gesellschaft für Humangenetik, ÖGH), the Austrian Society for Laboratory Medicine and Clinical Chemistry (Österreichische Gesellschaft für Labormedizin und Klinische Chemie, ÖGLMKC) and the Austrian Society für Genetics and Gene Technology (Österreichische Gesellschaft für Genetik und Gentechnologie, ÖGGGT).

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# FACTOR V LEIDEN

- **Background**

  The factor V Leiden polymorphism (1691G->A, R506Q) in the factor V gene (F5) is present in approximately 3% of the general population, and in about 20-50% of patients with a history of unexplained recurrent venous thrombosis. The presence of a glutamine (Q) instead of an arginine (R) residue removes a site in coagulation factor V that is normally cleaved by activated protein C, and is as-sociated with resistance to activated protein C. Presence of this polymorphism substantially increases the lifetime risk of venous thrombosis.

- **Factor V Leiden (F5 R506Q) genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| F5 RR | 92% | Wild type genotype.<br>No Factor V Leiden variant detectable. |
| F5 RQ | 8% | Heterozygous for factor V Leiden.<br>The relative risk of venous thrombosis is increased approximately 3- to 8-fold. |
| F5 QQ | < 0.1% | Homozygous for factor V Leiden.<br>The relative risk of venous thrombosis is increased approximately 20- to 80-fold. |

- **Indications for testing**

  According to the College of American Pathologists (CAP) Consensus Conference Statement, testing for factor V Leiden is recommended in patients with

  - a history of recurrent VTE, first VTE at younger than 50 years, or first unprovoked VTE at any age,
  - a first VTE at an unusual anatomic site, such as the cerebral, mesenteric, portal, or hepatic veins,
  - a first VTE, at any age, in a subject with a first degree family member with a VTE before the age of 50 years,
  - a first VTE related to pregnancy, the puerperium, oral contraceptive use, or hormone replacement therapy,
  - unexplained pregnancy loss during the second or third trimester.

**References:**

Renner W, Köppel H, Hoffmann C, Schallmoser K, Stanger O, Toplak H, Wascher TC, Pilger E. Prothrombin G20210A, factor V Leiden, and factor XIII Val34Leu: common mutations of blood coagulation factors and deep vein thrombosis in Austria. Thromb Res. 2000;99:35-9.





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# PROTHROMBIN 20210A

- **Background**

  The prothrombin (coagulation factor II) 20210A mutation is a common genetic risk factor for thrombosis and is associated with elevated prothrombin levels. Higher concentrations of prothrombin lead to increased rates of thrombin generation, resulting in excessive growth of fibrin clots.

- **Prothrombin (F2 20210G>A) genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| F2 GG : | 97% | Wild type genotype.<br>No prothrombin 20210A variant detectable. |
| F2 GA : | 3% | Heterozygous for prothrombin 20210A.<br>The risk of venous thrombosis is increased approximately 2- to 4-fold compared to the wildtype.. |
| F2 AA : | < 0.1% | Homozygous for prothrombin 20210A.<br>The risk of venous thrombosis is increased, although the magnitude is not well defined. |

- **Indications for testing**
  - a history of recurrent VTE, first VTE at younger than 50 years, or first unprovoked VTE at any age,
  - a first VTE at an unusual anatomic site, such as the cerebral, mesenteric, portal, or hepatic veins,
  - a first VTE, at any age, in a subject with a first degree family member with a VTE before the age of 50 years,
  - a first VTE related to pregnancy, the puerperium, oral contraceptive use, or hormone replacement therapy,
  - unexplained pregnancy loss during the second or third trimester.

**References:**

Renner W et al. Prothrombin G20210A, factor V Leiden, and factor XIII Val34Leu: common mutations of blood coagulation factors and deep vein thrombosis in Austria. Thromb Res 2000;99:35-9.

McGlennen RC et al. Clinical and laboratory management of the prothrombin G20210A mutation. Arch Pathol Lab Med. 2002 Nov;126(11):1319-25.




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# FACTOR XIII V34L

- **Background**

  In the final step of the clotting cascade, coagulation factor XIII is activated by thrombin-catalyzed cleavage of its activation peptide. Active Factor XIII generates covalent cross-linking of fibrin strands and conversion of soluble fibrin molecules into a stable insoluble clot. Factor XIII also participates in other physiologic processes, including clot retraction, cell migration, and wound healing.

  The gene for factor XIII (gene symbol F13) carries a common Val34Leu polymorphism, causing a change in amino acid structure of the polypeptide close to the thrombin cleavage site. The 34L variant has been associated with a reduced risk for venous thrombosis, coronary artery disease and stroke in several studies.

- **Factor XIII (F13 V34L) genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| F13 VV : | 53% | Wild type genotype. |
| F13 VL : | 39% | Heterozygous for F13 34L.<br>Modestlv reduced risk for venous thrombosis or coronary artery disease. |
| F13 LL : | 8% | Homozygous for F13 34L.<br>The risk for venous thrombosis or coronary artery disease is about 30% lower compared to the wild type genotype. |

- **Indications for testing**

  Estimation of individual risk for venous thrombosis or coronary artery disease.

**References:**


Renner W et al. Prothrombin G20210A, factor V Leiden, and factor XIII Val34Leu: common mutations of blood coagulation factors and deep vein thrombosis in Austria. Thromb Res 2000;99:35-9.

Wells PS et al. Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE review and meta-analysis. Am J Epidemiol. 2006;164:101-9.

Vokó Z, Bereczky Z, Katona E, Adány R, Muszbek L.Factor XIII Val34Leu variant protects against coronary artery disease. A meta-analysis. Thromb Haemost. 2007;97:458-63.







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# FIBRINOGEN-GAMMA POLYMORPHISM (FGG 10034C>T)

- **Background**

  Thrombin-induced conversion of fibrinogen to fibrin plays an essential role in hemostasis and results in the stabilization of thrombi. A C/T polymorphism at nucleotide 10034 of the fibrinogen gamma gene (FGG 10034C>T) leads to an alteration in the expression of fibrinogen gamma, without affecting total fibrinogen levels. This alteration results in an increased susceptibility to venous thrombosis.

- **Fibrinogen gamma (FGG 10034C>T) genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| FGG 10034 CC | 60% | Wild type genotype.<br>No FGG 10034T variant present detectable.. |
| FGG 10034 CT | 35% | Heterozygous for the FGG 10034T variant.<br>The risk for venous thrombosis is about 30% higher compared to the wild type genotype. |
| FGG 10034 TT | 5% | Homozygous for the FGG 10034T variant.<br>The risk of venous thrombosis is increased about 2-fold compared to the wild type genotype. |

- **Indications for testing**

  Estimation of individual risk for venous thrombosis.

**References:**

Grünbacher G et al. The fibrinogen gamma (FGG) 10034C>T polymorphism is associated with venous thrombosis. Thromb Res. 2007;121:33-6.

Uitte de Willige S et al. Genetic variation in the fibrinogen gamma gene increases the risk for deep venous thrombosis by reducing plasma fibrinogen gamma' levels. Blood. 2005;106:4176-83.




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# PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1)

- **Background**

  The type 1 plasminogen activator inhibitor (PAI-1) is a primary regulator of the fibrinolytic system in vivo. PAI-1 binds to tissue plasminogen activator and inhibits plasminogen activation, which decreases fibrinolysis. A single guanosine insertion/deletion (4G or 5G) 675 base pairs from the start site of the genes promoter region affects an individual's predisposition for thrombosis. Studies have shown a correlation between PAI-1 levels in plasma and the 4G/5G polymorphism. Subjects with the 4G/4G genotype have plasma PAI-1 concentrations that are 25% higher than those with the 5G/5G genotype. Increased PAI activity may be associated with increased risk for venous thrombosis and myocardial infarction. The prevalence of the 4G/4G genotype in the normal population is 26%.

- **Indications for testing**

  - Patients presenting with family histories of early heart disease or venous thrombosis
  - Pregnant women with past complications during pregnancy.

**References:**

Tsantes AE et al. Association between the plasminogen activator inhibitor-1 4G/5G polymorphism and venous thrombosis. A meta-analysis. Thromb Haemost. 2007;97:907-13.

Fabbro D et al. Association between plasminogen activator inhibitor 1 gene polymorphisms and preeclampsia. Gynecol Obstet Invest. 2003;56:17-22.





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# MTHFR 677T AND HOMOCYSTEINE

- **Background**

  Hyperhomocysteinemia is a widely recognized risk factor for coronary artery disease, venous thrombosis, and stroke. It is also involved in the pathogenesis of neural tube defects, stillbirths, and recurrent pregnancy loss. The leading cause of hyperhomocysteinemia is folate deficiency. Other determinants include insufficient B12 intake, impaired renal function, and genetic variations including those in the MTHFR gene. Folate supplementation can correct for most causes of hyperhomocysteinemia.

  Methlyenetetrahydrofolate reductace (MTHFR) is a key enzyme in the metabolism of homocysteine. Mutations in the MTHFR gene have been reported as causes of hyperhomocysteinemia. The most common MTHFR mutation, C677T, is present in the homozygous state in 5-10% of the general Caucasian population. In homozygous individuals, this results in a thermolabile variant of the enzyme with decreased activity.

- **MTHFR 677C>T genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| MTHFR 677 CC | 41% | Wild type genotype.<br>No MTHFR 677-T variant detectable. |
| MTHFR 677 CT | 47% | Heterozygous for the MTHFR 677-T variant.<br>Moderately reduced MTHFR enzyme activity. |
| MTHFR 677 TT | 12% | Homozygous for the FGG 10034T variant.<br>Reduced MTHFR enzyme activity. Increased risk for hyperhomocysteinemia, particularly when deficient in folate. |

- **Indications for testing**
  - Hyperhomocysteinemia
  - History of venous thromboembolism, coronary artery disease, and/or stroke
  - History of pregnancy complications including neural tube defects, stillbirths, and/or recurrent pregnancy loss

**References:**

Klerk M et al. MTHFR 677C->T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA. 2002;288:2023-31.

Den Heijer M et al. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. J Thromb Haemost. 2005:292-9.




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# HEREDITARY HEMOCHROMATOSIS (HFE GENE TEST)

- **Background**

  Hereditary hemochromatosis is characterized by inappropriately high absorption of iron by the gastrointestinal mucosa, resulting in excessive storage of iron particularly in the liver, skin, pancreas, heart, joints, and testes. Abdominal pain, weakness, lethargy, and weight loss are early symptoms. Without therapy, males may develop symptoms between age 40 and 60 years and females after menopause. Hepatic fibrosis or cirrhosis may occur in untreated individuals after age 40 years. Other findings in untreated individuals may include progressive increase in skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism.

  The diagnosis of hereditary hemochromatosis is typically based on the results of the screening tests transferrin-iron saturation and serum ferritin concentration, and of confirmatory tests such as molecular genetic testing for the C282Y and HFE H63D mutations in the HFE gene. About 87% of individuals of European origin with hereditary hemochromatosis are either homozygotes for the C282Y mutation or compound heterozygotes for the C282Y and H63D mutations.

- **HFE genotypes**

| HFE C282Y and H63D genotypes | Commentary |
|---|---|
| HFE 282 YY | This genotype is consistent with a diagnosis of hereditary hemochromatosis.<br>In asymptomatic patients, indices of iron overload (serum transferrin saturation and ferritin) should be monitored regularly |
| HFE 282 CY + HFE 63 HD (compound heterozygous) | This genotype is consistent with the presence of iron overload and may be diagnostic of hereditary hemochromatosis once all other reasons for iron overload have been excluded (e.g. alcohol consumption, hepatitis C, hyperferritinaemia). |
| All other genotypes: | All other HFE genotypes make a diagnosis of hereditary hemochromatosis very unlikely and such a diagnosis can only be made on a clinical basis. |

- **Indications for testing**

  - Confirmation of hereditary hemochromatosis in patients with elevated transferrin saturation or serum ferritin level
  - First-degree relative with hereditary hemochromatosis
  - First-degree relative with susceptibility to hereditary hemochromatosis (homozygosity for 282Y mutation or compound heterozygous for 282Y and 63D)

**References:**

Bomford A. Genetics of haemochromatosis. Lancet 2002; 360: 1673–81.

Yen AW et al. Revisiting Hereditary Hemochromatosis: Current Concepts and Progress. Am J Med 2006;119:391-9.





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# LACTOSE INTOLERANCE (LCT GENE TEST)

- **Background**

  Lactose intolerance (Adult type hypolactasia) is the inability to digest and absorb lactose (the sugar in milk), resulting in gastrointestinal symptoms when milk or products containing milk are drunk or eaten. In order for lactose to be absorbed from the intestine and into the body, it must first be split into glucose and galactose. The enzyme that splits lactose into glucose and galactose is called *lactase*, and it is located on the surface of the cells that line the small intestine. Lactose intolerance is caused by reduced or absent activity of *lactase* that prevents the splitting of lactose (lactase deficiency or hypolactasia).

- **Diagnosis of lactose intolerance**

  Usually, lactose intolerance was diagnosed by ingestion of pure lactose and measurement of hydrogen in the breath. Unfortunately, the hydrogen test lasts several hours and leads to strong abdominal symptoms in lactose intolerant patients.

  Recently, the genetic cause for the lactose intolerance was discovered. At the location -13910 before the lactase gene (LCT) there is a polymorphism, which determines the quantity of lactase produced. By testing the LCT genotype the genetic disposition for lactose intolerance can be determined.

- **LCT -13910 genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| LCT -13910 TT | 40% | No genetic disposition to lactose intolerance |
| LCT -13910 TC | 45% | No genetic disposition to lactose intolerance |
| LCT -13910 CC | 15% | Genetic disposition for lactose intolerance |

- **Indications for testing**

  Symptoms of lactose intolerance, such as abdominal pain, diarrhea, flatulence (passing gas), after ingestion of milk or dairy products.

**References:**

Hogenauer C, Hammer HF, Mellitzer K, Renner W, Krejs GJ, Toplak H. Evaluation of a new DNA test compared with the lactose hydrogen breath test for the diagnosis of lactase non-persistence. Eur J Gastroenterol Hepatol. 2005;17:371-6.




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# HEREDITARY FRUCTOSE INTOLERANCE (HFI) (FRUCTOSEMIA, ALDOLASE B DEFICIENCY)

- **Background**

  Hereditary fructose intolerance (HFI) is a hereditary condition caused by a deficiency of liver enzymes that metabolise fructose. The deficient enzyme is aldolase-B (ALDOB), which converts fructose-1-phosphate to DHAP and glyceraldehyde. This means that the fructose cannot be further metabolised beyond fructose-1-phosphate. The incidence of HFI in Europe is about 1:20.000..

- **Symptoms of HFI**

  Symptoms include severe abdominal pain, vomiting, and hypoglycemia following ingestion of fructose or other sugars metabolized through fructose-1-phosphate. Prolonged fructose ingestion in infants leads ultimately to hepatic and/or renal failure and death. Patients develop a strong distaste for sweet food, and can avoid a recurrence of symptoms chronic course of the disease by remaining on a fructose- and sucrose-free diet.

  HFI must not be confused with fructose malabsorption, which is a non-life threatening and much more common condition.

- **Causes of HFI**

  HFI is caused by mutations in the ALDOB gene, which encodes the enzyme Fructose-1-phosphate-aldolase-B. Depending on the type of mutation, enzymatic activity can be reduced by 85 to 100%.

- **Diagnosis of HFI**

  I: Genetic test for the most common ALDOB mutations ALDOB A149P, A174D and N334K. This test detects about 87% of ALDOB mutations in Europe.

  II: Complete sequence analysis of the ALDOB gene to detect rare mutations.

  Note: The $H_2$ breath test, which is a safe and noninvasive procedure for the diagnosis of fructose malabsorption, is not useful for the diagnosis of HFI.

**References:**

Santer et al., The spectrum of aldolase B (ALDOB) mutations and the prevalence of hereditary fructose intolerance in Central Europe. Hum Mutat. 2005;25:594.




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# ALPHA-1-ANTITRYPSIN (AAT) DEFICIENCY (SERPINA1 MUTATIONS)

- **Background**

  The protease inhibitor alpha-1-antitrypsin (AAT), found in high concentrations in the plasma, inhibits trypsin and also neutrophil elastase. AAT deficiency leads to an unchecked action of trypsin and elastase. Pulmonary emphysema, chronic obstructive pulmonary disease etc. are among the most common symptoms caused by an AAT deficiency. Furthermore, due to the toxic effect of the accumulated AAT on the liver cells, clinical pictures such as cirrhosis of the liver and even liver carcinoma are among other late sequelae.

- **Causes of AAT deficiency**

  The causes of AAT deficiency are mainly two variants of SERPINA1 gene, which encodes AAT. In contrast to normal alleles (M), the risk alleles Z and S are associated with considerably lower plasma concentrations of AAT. The Z variant is by far the most common and diagnostically significant deficient allele (in 95% of all patients with severe AAT deficiency) whereas heterozygous (MZ or SZ) and homozygous SS carriers as a rule only fall ill if there are additional risk factors involved such as smoking. With early diagnosis, patients can accordingly avoid negative factors, clinical late sequelae can be prevented or minimised. With an incidence of 1:2.000, AAT deficiency is one of the most common potentially lethal hereditary diseases in Europe.

- **SERPINA1 genotypes**

| Genotype | Commentary |
|---|---|
| MM, MS, SS | No Z-allele present.<br>AAT levels normal or only modestly reduced. |
| MZ, SZ | Heterozygous carrier of a Z-allele.<br>AAT-levels decreased by about 50% (MZ) to 70% (SZ). Modestly increased risk for AAT deficiency-related diseases of lung or liver. |
| ZZ | Homozygous carrier of a Z-allele.<br>AAT-levels strongly reduced. Without treatment, about 75% of carriers of this genotype will develop AAT deficiency-related diseases of lung or liver. |

**References:**

Luisetti, Epidemiology of alpha1-antitrypsin deficiency. Thorax 2004;59:164-9.




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# WILSON DISEASE
# (ATP7B H1069Q MUTATION)

- **Background**

  Wilson's disease is an autosomal-recessive disorder caused by mutation in the ATP7B gene, with resultant impairment of biliary excretion of copper. Subsequent copper accumulation, first in the liver but ultimately in the brain and other tissues, produces protean clinical manifestations that may include hepatic, neurological, psychiatric, ophthalmological, and other derangements.

  The most common mutation in patients from Central, Eastern, and Northern Europe is the point mutation H1069Q. About 50–80% of Wilson disease (WD) patients from these countries carry at least one allele with this mutation with an allele frequency ranging between 30 and 70%.

- **Indications for testing**

  Suspected diagnosis of Wilson's disease

**References:**

Ferenci, Regional distribution of mutations of the ATP7B gene in patients with Wilson disease: Impact on genetic testing. Hum Genet. 2006;120:151-9.




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# FAMILIAL DEFECTIVE APOLIPOPROTEIN B-100 (APOB 3500Q MUTATION)

- **Background**

  Familial defective apolipoprotein B-100 (FDB) is the most prevalent monogenic lipoprotein disorder in Central Europe and caused by mutations in the APOB gene encoding the apolipoprotein (apo) B-100 molecule. Apo B-100 is part of the LDL particle and mediates as ligand the uptake of the cholesterol-rich LDL particle into the cell. Cholesterol is elevated within the blood in patients with FDB, causing atherosclerotic changes and, as a consequence, heart attacks or cerebrovascular strokes.

  The most frequent mutation leading to familial defective apo B-100 is an arginin (R) to glutamin (Q) mutation at amino acid position 3500 (APOB R3500Q).

| Genotype | Commentary |
|---|---|
| APOB RR | Wildtype ("normal") ApoB-100 (no R3500Q mutation) |
| APOB RQ: | Heterozygous ApoB-100 R3500Q Mutation (frequency about 1:500) |
| APOB QQ: | Homozygous ApoB-100 R3500Q Mutation (very rare) |

- **Clinical consequences of the APOB R3500Q mutation**

  Carriers of an APOB R3500Q mutation are at strongly increased risk for hypercholesterolemia. The risk to develop heart attacks and cerebrovascular strokes is similar to that in familial hypercholesterolemia (LDL receptor mutations).

- **Indications for testing**

  - Hyperlipidemie (hypercholesterolemia)
  - First-degree relatives of patients with an APOB R3500Q mutation.

**References:**

Whitfield et al., Lipid disorders and mutations in the APOB gene. Clin Chem. 2004 50:1725-32.




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# APOE GENETICS

- **Background**

  Apolipoprotein E (ApoE) is a constituent of lowdensity lipoproteins (LDL) and mediates the transport of cholesterol from the liver into the body tissue. ApoE also performs numerous functions in addition to lipid metabolism, such as modulation of cellular immune response, inhibition of thrombocyte aggregation and regulation of steroid synthesis. In the peripheral nervous system ApoE influences growth and differentiation of neurons. As a result of this and the breaking down of neurotoxic amyloid-peptides and plaque compounds, ApoE is attributed a role in the pathogenesis of Alzheimer's disease.

  The human ApoE gene is located on chromosome 19 and occurs in three relatively common polymorphisms. The most common isoform Apo e3 has a single cysteine at position 112 and an arginine at position 158. Apo e2 contains 2 cysteine residues at these positions and Apo e4 two arginine residues. Depending on the combination, there are as many as six known different genotypes.

- **APOE Genotypes**

| Genotype group: | Genotypes (frequency) |
|---|---|
| Wildtype genotype | 3-3 (59%) |
| Carriers of e4 | 3-4 (23%), 4-4 (2%) |
| Carriers of e2 | 2-3 (12%), 2-2 (1%), 2-4 (2%) |

- **Clinical consequences of APOE genotypes**

  Compared to the wild type, ApoE2 has less affinity to the LDL receptor. This may result in hypercholesterolaemia and increased risk for cardiovascular disease.

  Carriers of an APOE e4 allele are at increased risk for Alzheimer's disease. Alzheimer's disease is a multifactorial disease and the presence of an e4 allele alone is not sufficient for the development of the disease. Nevertheless, ApoE genotyping may increase the specificity of clinical diagnosis and thus be helpful in Alzheimer diagnosis.

**References:**

Mahley et al., Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond. Curr Opin Lipidol. 1999;10:207-17.




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# COL1A1 POLYMORPHISM OSTEOPOROSIS-RISK

- **Background**

  Osteoporosis is one of the most common diseases in old age. The pathogenesis of osteoporosis is associated with many factors: genetic, environmental, biomechanical, chronic disease states, and the effects of endogenous hormones.

  One of the best examined candidate genes is COL1A1, which encodes the alpha-1 chain of type I collagen, the major protein of bone. A polymorphism (Sp1 polymorphism) in the COL1A1 gene is associated with bone mineral density and osteoporotic fracture risk.

- **COL1A1 2046G>T genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| COL1A1 2046 GG (SS): | 61% | Wildtype ("normal") genotype |
| COL1A1 2046 GT (Ss): | 36% | Heterozygous carrier of the Sp1 variant.<br>Modestly increased risk for osteoporosis.<br>Osteoporotic fracture risk 26% higher compared to the wildtype genotype |
| COL1A1 2046 TT (ss): | 3% | Homozygous carrier of the Sp1 variant.<br>Increased risk for osteoporosis.<br>Osteoporotic fracture risk 78% higher compared to the wildtype genotype |

- **Indications for testing**

  Determination of the COL1A1 genotype may help to assess to individual risk for osteoporosis. Preventive therapy in subjects at risk may help to reduce the risk for osteoporotic fractures.

**References:**

Mann V, Ralston SH. Meta-analysis of COL1A1 Sp1 polymorphism in relation to bone mineral density and osteoporotic fracture. Bone. 2003;32:711-7.




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Gene test information

# 5-FU TOXICITY (DPYD MUTATIONS)

- **Background**

  5-Fluorouracil (5-FU) is one of the most commonly prescribed anti-cancer agents and used for a wide variety of malignancies, including colorectal, gastric, pancreatic, head, neck, breast, ovarian, and cervical cancers.

  Dihydropyrimidine dehydrogenase (DPYD) is a key enzyme in the breakdown of 5-FU, and DPYD deficiency is an important determinant for severe adverse reactions from 5-FU treatment. Individuals with diminished DPYD activity cannot effectively inactivate 5-FU, which leads to toxic levels of 5-FU and to severe-to-lethal hematological, gastrointestinal, or neurological reactions, including stomatitis, diarrhea, dermatitis, fever, leukopenia, therombocytopenia, myelosuppression, and even death.

  More than 40 mutations in the gene that codes for DPYD have been described and the most common three of them (DPYD*2A, p.I560S, p.D949V) account for more than 50% of the patients with a complete or nearly complete DPD deficiency.

- **Indications for testing**

  - Estimation of individual risk for 5-FU toxicity
  - Analysis of the molecular cause for previous 5-FU toxicities

  Factors other than DPYD mutation can influence drug response. A negative result (no mutant DPYD allele detected) on this test does not completely exclude toxicities in patients treated with 5-FU.

**References:**

Morel A et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther. 2006;5:2895-904.




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# THIOPURIN TOXICITY (TPMT GENE TEST)

- **Background**

  The thiopurine drugs 6-mercaptopurine (6-MP), azathioprine (AZA) and thioguanine are widely used for the treatment of a variety of diseases, including childhood acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), inflammatory bowel disease, autoimmune hepatitis, rheumatic diseases, dermatologic conditions and in transplantation medicine. However, thiopurine drugs have a relatively narrow therapeutic index and are capable of causing life-threatening toxicity, most often myelosuppression.

  Thiopurine S-methyltransferase (TPMT), an enzyme metabolizing these drugs, exhibits a genetic polymorphism. This polymorphism causes leads to reduced TPMT activity in 10% of Caucasians and complete TPMT deficiency in about 1/300 individuals.

  In Caucasians, three common TPMT gene variants (*2, *3A, *3C) are associated with diminished TPMT activity. Analysis of TPMT genotypes can help to predict the individual risk for thiopurine toxic side effects.

- **TPMT genotypes**

| Class | Frequency | Genotypes (examples) | Commentary |
|---|---|---|---|
| No TPMT Deficiency | 89% | *1*1 | No sign for reduced TPMT activity (wild-type genotype) |
| Heterozygous deficiency | 11% | *1*2, *1*3A, *1*3C | Reduced TPMT activity |
| Homozygous deficiency | 0.3% | *3A*3A, *3A*3C, *3A*2A | Deficient TPMT activity. |

- **Indications for testing**

  Estimation of individual risk for thiopurine toxicity

**References:**

Sahasranaman S et al. Clinical pharmacology and pharmacogenetics of thiopurines. Eur J Clin Pharmacol. 2008;64:753-67.




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# PHARMACOGENETICS OF COUMARINS (VKORC1 AND CYP2C9 GENE TESTS)

- **Background**

  Coumarins, such as warfarin and phenprocoumon, are vitamin K agonists that have been widely used as orally administered anticoagulants for therapy and prophylaxis of thromboembolic conditions. Due to its narrow effective therapeutic concentration ranges and broad variation in required individual dosage, clinical management of coumarin therapy may be demanding.

  Vitamin K epoxide reductase (VKORC1), the main target of coumarins, carries a common G/A polymorphism which plays an important role in coumarin dose. Additionally, cytochrome CYP2C9 is essential for the metabolism of coumarins. Defective CYP2C9 gene variants (*2, *3) lead to reduced enzymatic degradation of coumarins, resulting in lower coumarin dosages and an increased tendency to severe overanticoagulation and retarded stabilization.

- **VKORC1 genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| VKORC1 -1639 GG | 38% | Lower coumarin sensitivity<br>(higher dosage of coumarin may be required) |
| VKORC1 -1639 GA | 43% | Normal coumarin sensitivity |
| VKORC1 -1639 AA | 19% | Higher coumarin sensitivity<br>(lower dosage of coumarins may be required) |

- **CYP2C9 genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| CYP2C9 *1*1 | 67% | Wild-type genotype |
| CYP2C9 *1*2 or *1*3<br>(heterozygous deficiency) | 29% | Heterozygous CYP2C9 deficiency<br>(Lower dosage of coumarins may be required, increased risk for over-anticoagulation) |
| CYP2C9 *2*2, *2*3, *3*3<br>(homozygous deficiency) | 4% | Homozygous CYP2C9 deficiency<br>(Lower dosage of coumarins may be required, increased risk for over-anticoagulation) |

- **Indications for testing**

  - Individuals starting coumarin therapy
  - Individuals receiving coumarin therapy, without achieving an acceptable stable international normalized ratio (INR).

**References:**

Oldenburg J et al. Current pharmacogenetic developments in oral anticoagulation therapy: The influence of variant VKORC1 and CYP2C9 alleles. Thromb Haemost. 2007;98:570-578.





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# CLOPIDOGREL-RESISTANCE (CYP2C19 GENE TEST)

- **Background**

  Clopidogrel (Plavix) inhibits platelet aggregation and is used in the management of patients with coronary artery disease, with acute coronary syndromes, and/or after percutaneous coronary interventions. Clopidogrel is an inactive pro-drug that requires hepatic activation cytochrome P450 2C19 (CYP2C19).

  A number of different alleles of CYP2C19 have been identified; depending on the allele present, laboratory demonstrations of the enzymatic activity of CYP2C19 can be normal, reduced, or increased. Patients with reduced CYP2C19 activity have less formation of clopidogrel's active metabolite and demonstrate reduced clopidogrel-induced platelet inhibition.

- **CYP2C19 genotypes**

| Genotype | Type | Frequency | Commentary |
|---|---|---|---|
| *1**1 | Extensive metabolizer | 71% | No sign of reduced CYP2C19 activity. |
| *1*2, *1*3 | Intermediate metablizer | 26% | Reduced CYP2C19 activity.<br>Reduced effectiveness of clopidogrel. |
| *2*2, *3*3, *2*3 | Poor metabolizer | 3% | Strongly reduced CYP2C19 activity.<br>Reduced effectiveness of clopidogrel. |

- **Indications for testing**

  Individuals starting or clopidogrel therapy

**References:**

Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009;302:849-57.




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Gene test information

# SIDE-EFFECTS of STATINS (SLCO1B1 GENE TEST)

- **Background**

  Statins are well established drugs for the treatment of hypercholesterolaemia and the prevention of atherosclerosis and related coronary heart disease. Treatment with statins leads to significant low-density lipoprotein cholesterol (LDL) lowering, reducing major coronary and vascular events. Although statins are generally well tolerated and safe; there is wide inter-individual variability in response to statin therapy, in terms of both lipid-lowering and adverse drug reactions.

  The most common adverse effect of statin therapy is myopathy, ranging from mild myalgia to severe rhabdomyolysis. In observational studies, myopathies occur in 10% - 20% of patients taking statins. For most statins, both efficacy and risk of adverse muscle events is influenced by membrane transporters, which are important determinants of statin disposition. The hepatic uptake of statins from portal blood is mediated by a influx transporter encoded by the SLCO1B1 gene. A common haplotype, SLCO1B1*5, which can be tagged by the Val174Ala polymorphism, interferes with localization of the transporter and leads to greater systemic statin concentrations and an increased risk for myopathies.

- **SLCO1B1 V174A genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| VV | 70% | Normal SLCO1B1 activity. |
| VA | 28% | Intermediate SLCO1B1 activity.<br>Increased risk for statin-induced myopathy. |
| AA | 2% | Low SLCO1B1 activity.<br>Strongly increased risk for statin-induced myopathy. |

- **Indications for testing**
  - Individuals starting statin therapy
  - Individuals suffering from myopathy during statin therapy.

**References:**

Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010;87:130-3.




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# PHARMACOGENETICS OF TAMOXIFEN (CYP2D6 GENE TEST)

- **Background**

  Tamoxifen, a molecule essentially prescribed for the treatment of breast cancer, is a pro-drug which must be activated by the enzyme CYP2D6 before becoming pharmacologically active. In post-menopausal women, CYP2D6 can become an indirect indicator of the after-effects of primary breast cancer being treated with tamoxifen.

- **CYP2D6 genotypes**

| Class | Frequency | Genotypes (examples) | Commentary |
|---|---|---|---|
| Extensive metabolizer (EM) | 92% | *1*1, *1*4, *1*3 | No sign of reduced CYP2D6 activity |
| Poor metabolizer (PM) | 8% | *4*4, *4*6, *3*4 | Strongly reduced CYP2D6 activity |

  The gene tests includes the most important non-functional CYP2D6 alleles (*3, *4, *6).

- **Indications for testing**

  Individuals starting tamoxifen therapy.

**References:**

Punglia RS, Burstein HJ, Winer EP, Weeks JC. Pharmacogenomic variation of CYP2D6 and the choice of optimal adjuvant endocrine therapy for postmenopausal breast cancer: a modeling analysis. J Natl Cancer Inst. 2008;100:642-8.

Goetz MP, Kamal A, Ames MM. Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. Clin Pharmacol Ther. 2008;83:160-6.




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Gene test information

# MTHFR 677T UND METHOTREXATE TOXICITY

- **Background**

  Methotrexate is an antimetabolite drug used in treatment of cancer and autoimmune diseases. As a structural analogue of folate, methotrexate interferes with folate metabolism by inhibiting dihydrofolate reductase, which leads to depletion of cellular folate. Supplementation with folate or folinic acid (leucovorin) reduces the efficacy and toxicity of methotrexate.

  MTHFR is an important enzyme in maintaining cellular folate pools, and MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia may affect methotrexate sensitivity and contribute to toxicity.

  A common MTHFR mutations, 677C>T, results in reduced MTHFR enzymatic activity. Heterozygous carriers of a 677T variant have approximately 60 percent of normal MTHFR enzyme normal activity. Homozygotes for 677T have about 30 percent of MTHFR enzyme activity. Carriage of MTHFR 677T variants has been associated with increased risk for methotrexate toxicities.

- **MTHFR genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| MTHFR 677 CC : | 41% | Wild-type ("normal") genotype.<br>No MTHFR 677T allele detected. |
| MTHFR 677 CT : | 47% | Heterozygous carrier of a MTHFR 677T allele.<br>Modestly increased risk for methotrexate toxicity |
| MTHFR 677 TT : | 12% | Homozygous carrier of two MTHFR 677T alleles.<br>Increased risk for methotrexate toxicity |

- **Indications for testing**

  Estimation of individual risk for methotrexate toxicity

**References:**

Hider SL et al. The pharmacogenetics of methotrexate. Rheumatology 2007;46:1520-4.





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# HLA B27

- **Background**

  Ankylosing spondylitis is a chronic rheumatic disease which primarily affects the spine. The early symptomatology of the disease leads to movement limitations of the lumbar spine. Further on in the course of the disease, the symptoms may worsen to the point of hardening of the bones of the spine.

  The fist signs of the disease are frequently nonspecific and are generally not associated with the disease. There is generally a time period of 5-10 years between the initial symptoms and a definite diagnosis. However, an early diagnosis is of crucial importance, since the course of the disease can be influenced better when the disease is diagnosed early on.

  The majority (>90%) of patients with ankylosing spondylitis carry the HLA-B27 gene, which however is only present in 8% of the “healthy” population. Thus the molecular genetic detection of HLA-B27 has a high diagnostic significance for the probability of developing ankylosing spondylitis.

- **Indications for testing**

  - Suspected clinical diagnosis of ankylosing spondylitis and/or related spondyloarthropathy
  - Inflammatory back pain for more than 3 months
  - Limitation of motion of the lumbar spine and/or of chest expansion
  - History of enthesitis, asymmetric arthritis, anterior uveitis, irritable bowel disease, and/or aortic insufficiency
  - Ambiguous result from flow cytometry for HLA-B27
  - Family history of ankylosing spondylitis

**References:**

Ramos M, López de Castro JA. HLA-B27 and the pathogenesis of spondyloarthritis. Tissue Antigens. 2002;60:191-205.

Suhler EB, Martin TM, Rosenbaum JT. HLA-B27-associated uveitis: overview and current perspectives. Curr Opin Ophthalmol. 2003;14:378-83.




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# CELIAC DISEASE

# (HLA-DQA1 and HLA DQB1 GENE TESTS)

- **Background**

  Celiac disease is a common enteropathy with a strong genetic risk. it is characterized by a permanent intolerance for gluten proteins present in dietary wheat, rye, and barley. It affects approximately 1:100–300 individuals, although only 1 person in 8 is aware of being affected because the symptoms may be mild or nonspecific.

  Environmental, genetic, and immunologic factors are important in the pathogenesis of celiac disease. Celiac disease is strongly associated with specific HLA-DQ2 and HLA-DQ8 molecules, encoded by HLA-DQA1 and HLA-DQB1 genes.

  A negative gene test for HLA-DQA1 and HLA-DQB1 variants associated with celiac disease effectively rules out a diagnosis of celiac disease. Nevertheless, the gene test on its own cannot diagnose celiac disease, only a small fraction of subjects with a positive gene test will develop celiac disease.

- **Possible test results**

| Test result | Commentary |
|---|---|
| Negative | No HLA-DQA1 and HLA-DQB1 variants associated with celiac disease were detected. A diagnosis of celiac disease can be ruled out with very high probability (>99%). |
| Positive | Detection of HLA-DQA1 and HLA-DQB1 variants associated with celiac disease. A diagnosis of celiac disease can not be ruled out. |

**References:**

Wolters VM. Genetic Background of Celiac Disease and Its Clinical Implications. Am J Gastroenterol 2008;103:190-5.





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# COMPLEMENT FACTOR H (CFH) AND AGE-RELATED MACULAR DEGENERATION (AMD)

- **Background**

  Age-related macular degeneration (AMD) is a disease that causes progressive damage to the macula. Macula is the central part of the retina that allows us to see fine details. When the macula degenerates, people experience blurring or darkness in the center of their vision. Macular degeneration leads to loss of central vision needed for activities requiring fine vision such as reading, driving and recognising faces.

  Complement factor H (CFH) gene has been determined to be strongly associated with a person's risk for developing AMD. A tyrosine (Y) to histidine (H) change at amino acid 402 in complement factor H results in the formation of a CFH gene variant. People whose genetic makeup includes this variant of the CFH gene are more likely to develop AMD.

- **CFH genotypes**

| Genotype | Frequency | Commentary |
|---|---|---|
| CFH 402 YY : | 63% | Wild-type ("normal") genotype.<br>No increased risk for AMD |
| CFH 402 YH : | 32% | Heterozygous carrier of a 402H allele.<br>Risk for AMD increased about 4-fold compared to wild-type genotype.. |
| CFH 402 HH : | 5% | Homozygous carrier of two 402H alleles.<br>Risk for AMD increased about 12-fold compared to wild-type genotype. |

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- **Indications for testing**

  - Estimation of individual risk for AMD

  - Optimization of therapy in AMD patients

**References:**

Wegscheider BJ, Weger M, Renner W, et al. Association of complement factor H Y402H gene polymorphism with different sub-types of exudative age-related macular degeneration. Ophthalmology. 2007;114:738-42.

Montezuma SR, Sobrin L, Seddon JM. Review of genetics in age related macular degeneration. Semin Ophthalmol. 2007;22:229-40.




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# FAMILIAL MEDITERRANEAN FEVER (MEFV GENE TEST)

- **Background**

  Familial Mediterranean fever (FMF), also called recurrent polyserositis, is characterized by brief recurrent episodes of peritonitis, pleuritis, and arthritis, usually with accompanying fever. FMF occurs within families and is much more common in individuals of Mediterranean descent than in persons of any other ethnicity. Nonsense or missense mutations in the MEFV gene appear to cause the disease in most cases.

  The diagnosis is clinically made on the basis of the history of typical attacks, especially in patients from the ethnic groups in which FMF is more highly prevalent. An acute phase response is present during attacks, with high C-reactive protein levels, an elevated white blood cell count and other markers of inflammation.

  Additionally, diagnosis of FMF can be confirmed by a genetic test that detects mutations in the MEFV gene. Sequencing of exons 2, 3, 5, and 10 of this gene are required to detect disease-associated mutations.

**References:**

Yepiskoposyan L, Harutyunyan A. Population genetics of familial Mediterranean fever: a review. Eur J Hum Genet. 2007;15:911-916.




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# SPECIMEN SHIPPING

- **How can I order a genetic test?**

  To request a gene test, please fill out the request form and send the form together with 5 ml EDTA blood (lavender tube) to the Labor Renner. The request form must be signed by a physician. It is not necessary to centrifuge the tube or refrigerate the specimen during transport.

- **How long will I have to wait for test results?**

  Test results will usually be available within 1 week of specimen receipt.

- **Will the costs for the genetic tests be covered by my regional or national health plan?**

  Labor Renner can not bill your health insurance plan directly. You must pay for the test and then seek reimbursement from your employment or private health care plan, if applicable.




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