MEDICOVER
GENETICS

CATALOGUE

CARDIAC AND AORTIC PANELS

Know&Manage

Physician Information

MEDICOVER GENETICS
ABOUT US

Medicover Genetics was developed as a strategic business area within Medicover, **a network of hospitals and diagnostic laboratories across 10 European markets**. Our purpose is to empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey, fueled by our vision to place genetics at the core of medical decisions. We want to achieve this by leveraging advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being.

Spanning cytogenetic analyses, molecular pathology solutions, the latest in next generation sequencing (NGS) technology and microbiome sequencing, Medicover Genetics offers a **complete in-house and tailor-made portfolio produced in our laboratories in Germany** and offered internationally. Medicover is the sole testing site in Europe for Bionano's Saphyr® technology: the third-generation optical mapping solution which resolves large-scale structural variations currently missed by NGS.

Using a robust diagnostics pipeline, we make **NGS testing and variant discovery efficient**, scalable and accessible by converting NGS data into customized clinical reports in a timely manner, **thereby decreasing turnaround times**.

Patient support through genetic counselling is integral to our patient journey and crucial to explain complex findings to them as well as assist physicians as they support their patients. With more than **20 certified genetic counsellors** across our markets, we are able to provide this locally and in the local language.

MEDICOVER GENETICS

PURPOSE

To empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey

VISION

To place genetics at the core of medical decisions

MISSION

Leverage advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being

VALUES

Humanity | Passion | Innovation | Medical Excellence | Integrity

MEDICOVER GENETICS
WHY US

- A network of laboratories and medical institutions makes Medicover Genetics **a leader in genetic testing** in Germany with foundations dating back to 1998

- A clinical team comprised of scientists, physicians and medical geneticists, several with **>20 years of experience** in genetic testing, assuring meaningful and comprehensive genetic tests

- **Up-to-date diagnostic algorithms** and gene panels based on current scientific literature and international guidelines

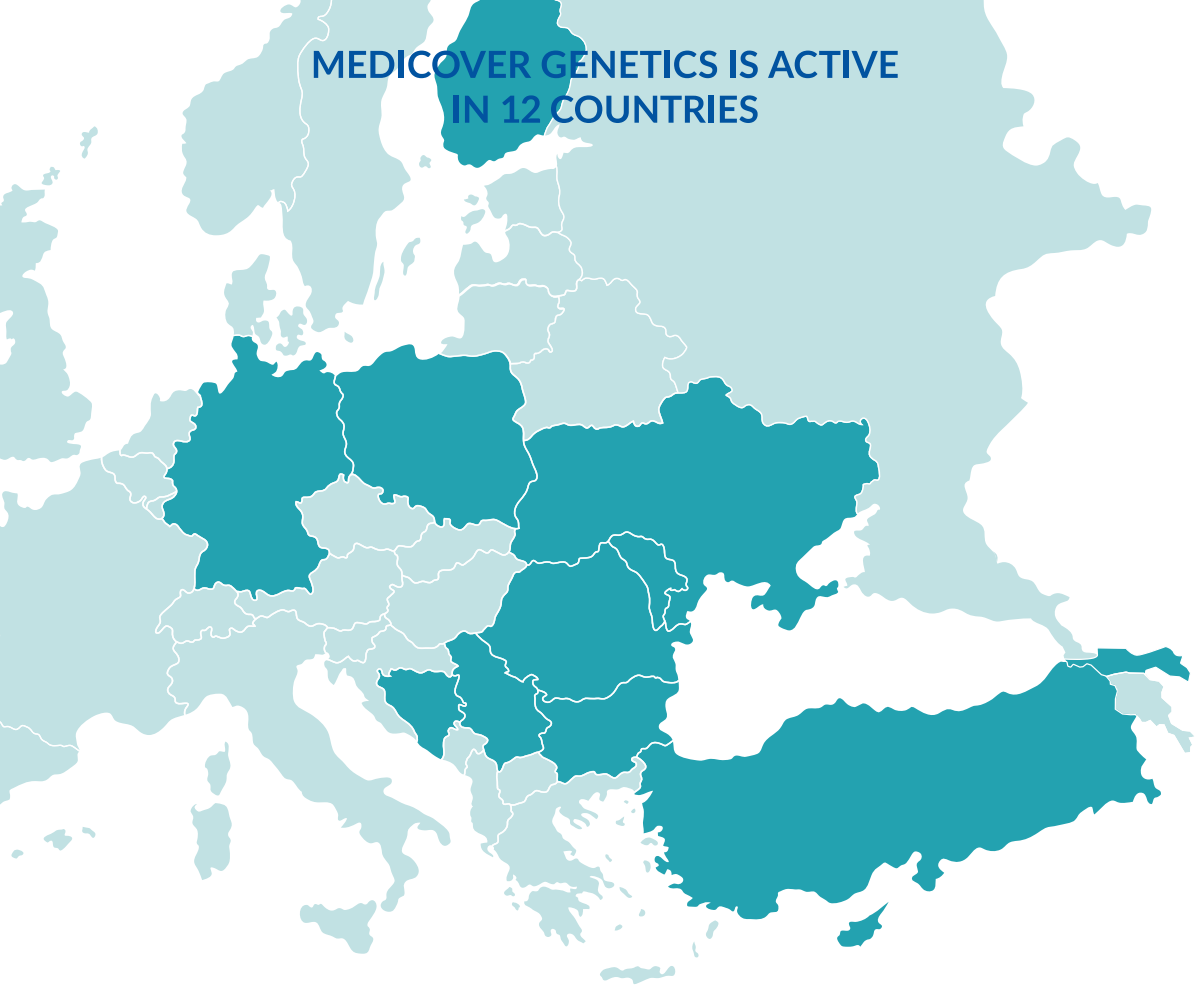
- Expertise in gene variant analysis ensuring "**no variant left behind**"

- Cutting-edge technology in sequencing and laboratory methods allows for **short turnaround times**

- **Quality** assessed by several certified bodies, including EFI, DIN EN ISO 9001, DIN EN ISO15189 accreditation for medical laboratories, DIN EN ISO/IEC 17025 accreditation for testing and calibration laboratories and a generally valid GMP (Good Medical Practice) certificate

- **Data privacy** is your right and our priority

MEDICOVER GENETICS IS ACTIVE IN 12 COUNTRIES



BOSNIA-HERZEGOVINA | BULGARIA | CYPRUS | FINLAND | GEORGIA
GERMANY | MOLDOVA | POLAND | ROMANIA | SERBIA | TURKEY | UKRAINE

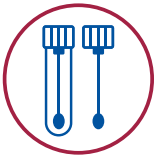
MEDICOVER GENETICS
TABLE OF CONTENTS

TECHNICAL INFORMATION

Technology	Next generation sequencing, Illumina NovaSeq6000
Gene Coverage & Depth	>95% of the exome yields at least 20X sequence depth with 5bp into flanking introns
Single Nucleotide Variant (SNV) Sensitivity	99.93%
Insertions/Deletions (Indel) Detection	Up to 21bp
Indel Sensitivity	95.32%
Indel Precision	94.71%
Human Reference Genome	GRCh38
Pathogenic Variant Confirmation	Sanger sequencing (only if quality falls below our criteria) of pathogenic or likely pathogenic variants
Variant Classification	According to ACMG guidelines

HOW TO ORDER

STEP 1
TEST ORDERED
Patient visits specialist to find the right test



STEP 2
SAMPLE COLLECTED
Sample collected at nearest blood drawing point

STEP 3
SAMPLE PROCESSED
Sequencing is performed in Germany

STEP 4
RESULTS DELIVERED
Report is delivered to you and your patient

GENETIC COUNSELLING

Genetic counselling by our local Medicover counsellors is available upon request

MATERIAL REQUIRED

1 ml EDTA blood sample or 1 Medicover Genetics Buccal Swab Kit

TURNAROUND TIME

15-25 working days

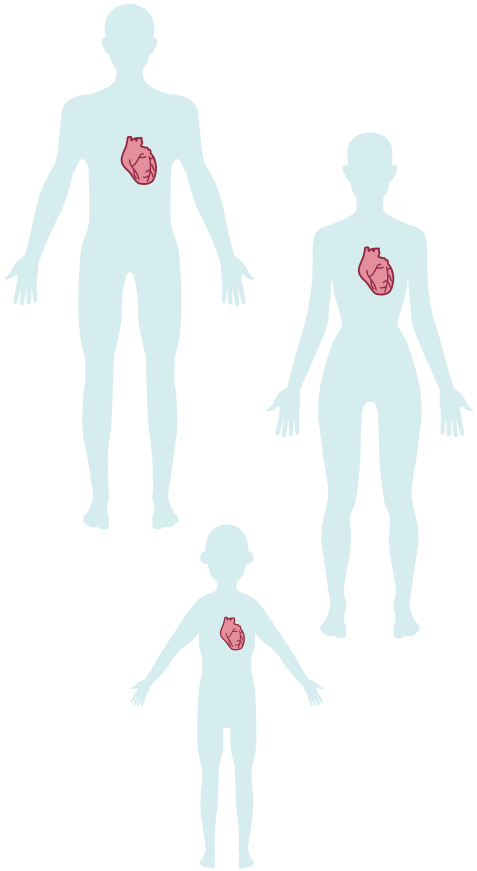
For complete information about our panels, including technical information and gene list, please visit: https://www.medicover-genetics.com

CARDIAC AND AORTIC PANELS
OVERVIEW

BACKGROUND

Hereditary cardiac disorders have a prevalence of 3% in the population. Arrythmogenic diseases are responsible for most cardiac mortality in the young, and congenital heart defects are the most common type of birth defect (1% of all live births). Owing to improved treatment and management options, there are more adults living with congenital heart defects than children. Importantly, deaths from aortic aneurysms may be prevented if individuals at risk are identified and managed. Many cardiac and aortic disorders show overlapping cardiac and non-cardiac symptoms, and genetic testing can help with a differential diagnosis in those cases.

Genetic information can improve clinical management by determining the right treatment and follow-up plan. It can predict a prognosis and therapy response and in some cases identify gene therapy options. Knowing about a cardiac or aortic disorder allows you to be proactive about your health with management strategies, such as medication, lifestyle changes or surgery.



TARGET POPULATION

People with a **family history** of unexplained cardiac arrest, cardiac death or sudden aortic events

Patients with a clinical diagnosis of a heart defect who **need a differential diagnosis**

A child **born with heart defects**, such as structural abnormalities of the heart muscle

A **child with neurodevelopmental delay** who might have a hereditary heart disorder

Patients who need prophylactic aortic surgery who want to **determine the right timing**

Patients with a hereditary heart disorder who want to estimate **the risk of a pregnancy**

CARDIAC AND AORTIC DISORDERS
OUR PANELS

Medicover Genetics offers comprehensive and syndrome-specific panels testing for cardiac and aortic disorders. The test can offer a molecular genetic diagnosis of a cardiac or aortic disorder that is observed or predicted in your patient.

ARRYTHMIAS & CARDIOMYOPATHIES

Disorders included: • Brugada Syndrome • Catecholaminergic Polymorphic Ventricular Tachycardia • Short QT Syndrome • Long QT Syndrome • Arrythmogenic Right Ventricular Cardiomyopathy • Dilated Cardiomyopathy • Hypertrophic Cardiomyopathy • Restrictive Cardiomyopathy • Left Ventricular/Noncompaction Cardiomyopathy

80 genes — Comprehensive Arrythmias & Cardiomyopathies

9 genes Brugada Syndrome	**8 genes** Catecholaminergic Polymorphic Ventricular Tachycardia	**6 genes** Short QT Syndrome
11 genes Long QT Syndrome	**8 genes** Arrythmogenic Right Ventricular Cardiomyopathy	**66 genes** Dilated Cardiomyopathy
60 genes Hypertrophic Cardiomyopathy	**6 genes** Restrictive Cardiomyopathy	**10 genes** Left Ventricular/ Noncompaction Cardiomyopathy

CONGENITAL HEART DEFECTS

Disorders included: • Adams-Oliver Syndrome • Char Syndrome • CHARGE Syndrome • Cornelia-de-Lange Syndrome • Costello Syndrome • Loeys-Dietz Syndrome • Noonan Syndrome • Alagille Syndrome • RASopathies With Heart Defects • Heterotaxy

91 genes	Comprehensive Congenital Heart Defects
2 genes	Alagille Syndrome
16 genes	RASopathies With Heart Defects
37 genes	Syndromic Congenital Heart Defects
22 genes	Isolated Congenital Heart Defects
5 genes	Heterotaxy

AORTIC DISORDERS

Disorders included: • Thoracic Aortic Aneurysms And Aortic Dissections • Bicuspid Aortic Valve • Cutis Laxa • Ehlers-Danlos Syndrome • Marfan Syndrome • Marfan-Like Disorders

37 genes	Comprehensive Aortic Disorders
29 genes	Ehlers-Danlos Syndrome
3 genes	Marfan Syndrome
12 genes	Marfan-Like Disorders

ARRYTHMIAS & CARDIOMYOPATHIES
COMPREHENSIVE PANEL

BACKGROUND

Arrythmogenic diseases are diseases of the heart muscle (cardiomyopathy) and diseases altering the heart rhythm (arrythmia). The most important cardiomyopathies are hypertrophic cardiomyopathy, dilated cardiomyopathy and arrythmogenic right ventricular cardiomyopathy. The three most common syndromes are long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. Most forms of these diseases follow an autosomal dominant inheritance pattern with incomplete penetrance and variable expression.

As the most important pathogenic genes are known for those syndromes, genetic diagnosis is useful to confirm the diagnosis and may have prognostic or therapeutic significance. The targeted analysis of family members is recommended if a pathogenic variant is identified in the index patient. Predictive diagnostics is also recommended for minors with a family history of hereditary arrythmogenic disease due to the therapeutic benefits.

GENE PANEL

80 genes

ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CALR3, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, FHL1, FKTN, FLNC, GLA, GPD1L, HCN4, ILK, JPH2, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNH2, KCNJ2, KCNJ8, KCNQ1, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, PKP2, PLN, PRDM16, PRKAG2, RAF1, RANGRF, RBM20, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN5A, SGCD, TAZ, TCAP, TECRL, TGFB3, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TRPM4, TTN, VCL

SYNDROMES INCLUDED

- Arrythmogenic right ventricular cardiomyopathy
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Isolated congenital heart defects
- Long QT syndrome
- Left ventricular/noncompaction cardiomyopathy
- RASopathies with heart defects
- Restrictive cardiomyopathy
- Short QT syndrome

POSSIBLE SYMPTOMS

- Irregular heartbeat (arrythmia)
- Sudden cardiac arrest/death
- Palpitations
- Fainting
- Chest pain
- Shortness of breath
- Exercise intolerance
- Fatigue
- RASopathies

TARGET POPULATION

People with a **family history** of unexplained cardiac arrest or cardiac death

Patients with a clinical diagnosis of a heart defect who **need a differential diagnosis**

Patients with a hereditary heart disorder who want to estimate **the risk of a pregnancy**

ARRYTHMIAS
BRUGADA SYNDROME PANEL

BACKGROUND

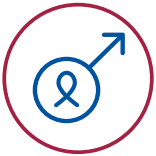
Brugada syndrome (BrS) is one of the most common causes of sudden cardiac death (SCD). It is responsible for about 20% of cases involving a structurally unrecognizable heart with men being affected about eight to ten times more frequently. The first symptoms can occur in early childhood, although they typically appear at the age of 30-40 years. In up to 25% of cases, pathogenic variants can be detected in the *SCN5A* gene, which lead to BrS type 1. Our panel includes *SCN5A* as well as other pathogenic variants in the calcium ion channel genes.

A characteristic feature of BrS is the ST segment elevation persisting in the right precordial ECG lead (BrS type I ECG), which in some cases can only be unmasked by antiarrythmic drugs such as ajmalin or flecainide. There is a predisposition to rapid polymorphic ventricular tachycardia and ventricular fibrillation. The symptoms often occur at night and often lead to SCD. The risk of SCD is 2-15%/year depending on the clinical symptoms.

GENE PANEL

9 genes CACNA1C, CACNB2, GPD1L, HCN4, KCNE3, SCN1B, SCN3B, SCN5A, TRPM4

One of **most common causes of SCD**

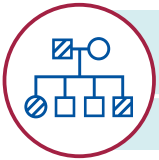


Men are **8-10x more affected**

Pathogenic **variants in *SCN5A* gene** found in up to 25% cases

In 1-10% of cases with BrS type I ECG, other forms of BrS are present. Some patients carry pathogenic variants in the calcium ion channel genes *CACNA1C* and *CACNB2*. In about 70% of all cases, no pathogenic variant can be detected. The combination of frequent polymorphisms seems to be associated with an up to 20-fold increased risk of BrS.

Current guidelines recommend implantable cardioverter defibrillator (ICD) implantation in all BrS patients with previous arrythmia-related symptoms. Additional treatment with quinidine has been shown to be useful in patients with multiple ICD shocks and electrical storms or in children at risk. In high-risk patients, catheter ablation (e.g., of the epicardium of the right ventricular outflow tract) should be considered, which not only reduces the occurrence of arrythmias, but can also eliminate the BrS-typical ECG pattern.



PREVALENCE	INHERITANCE PATTERN
1:5,000 to 1:10,000	Autosomal dominant

ARRYTHMIAS
CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA PANEL

BACKGROUND

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disease of the healthy cardiac muscle. The arrythmias are adrenergically induced and manifest on average at the age of 8. If left untreated, CPVT leads to syncope before the age of 40 in 60% of cases and to sudden cardiac death before the age of 30 in 30-50% of cases.

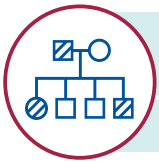
Bidirectional or polymorphic ventricular tachycardias are typical for CPVT. The resting ECG seems normal. The younger the patient when syncope occurs, the worse the prognosis; additionally the risk of cardiac events is about four times higher in men.

Pathogenic variants in the *RYR2* gene have been identified in 40-70% of CPVT patients. Rare variants in the *CASQ2* and *TECRL* genes are detectable in about 3-5% of patients and lead to an autosomal recessive inherited form of CPVT. *RYR2* gene, which codes for a cardiac ryanodine receptor, plays a central role in the activation of cardiomyocytes.

The therapy is beta-blockers. However, about 30% of patients remain symptomatic and may need an implanted defibrillator.

GENE PANEL

8 genes CALM1, CALM2, CALM3, CASQ2, KCNJ2, RYR2, TECRL, TRDN



PREVALENCE	INHERITANCE PATTERN
1:5,000 to 1:10,000	Autosomal dominant

ARRYTHMIAS
SHORT QT SYNDROME PANEL

BACKGROUND

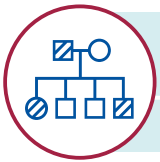
Cardiac events can occur in patients with short QT syndrome (SQTS) at any age; however, they are most common in the early years of life and in old age. The cumulative probability of suffering a cardiac arrest in the fifth decade of life is about 40%, which highlights the importance of early detection. The diagnostic sensitivity of molecular genetic screening in SQTS is currently about 15-25% and as a result, genetic testing is only recommended where there is a positive family history.

SQTS is characterized by a short QT interval reflecting shortened ventricular repolarization. In long-term ECG, a shortened frequency-corrected QT interval (QTc) of <340-350 ms and high or peaked T-waves can be detected, which greatly increases the risk of syncope, ventricular tachycardia and sudden cardiac death.

Pathogenic variants in cardiac potassium channel genes (*KCNQ1*, *KCNH2* and *KCNJ2*) can be detected in about 70% of molecular genetic positive SQTS cases. These variants lead to increased potassium currents, which means that the normal heart rhythm can no longer be maintained. In rare cases, loss-of-function variants in calcium channel genes (*CACNA1C*, *CACNB2* and *CACNA2D1*) are detected.

GENE PANEL

6 genes CACNA1C, CACNA2D1, CACNB2, KCNH2, KCNJ2, KCNQ1



PREVALENCE	INHERITANCE PATTERN
1:10,000 (Caucasian population)	Autosomal dominant

ARRYTHMIAS
LONG QT SYNDROME PANEL

BACKGROUND

Long QT syndrome (LQTS) is a clinically and genetically heterogeneous heart disease. A distinction is made between the very rare autosomal recessive Jervell-Lange-Nielsen (JLN) form and the more frequent autosomal dominant Romano-Ward (RW) form. The identification of carriers of pathogenic variants enables timely, possibly presymptomatic, therapy. The risk for cardiac events is thus reduced by 62-95% for LQTS type 1 and 74% for LQTS type 2. Pathogenic variants in one of the three genes *KCNQ1*, *KCNH2* and *SCN5A* are detected in about 90-95% of molecular genetic positive LQTS cases. However, in about 25% of clinically confirmed LQTS cases, no genetic cause can be found.

LQTS is characterized by a long QT interval reflecting prolonged ventricular repolarization. An extended frequency-corrected QT interval (QTc) of 460 to >500 ms can be demonstrated in long-term ECG. Depending on the QTc, arrythmias occur, which can lead to unconsciousness and sudden cardiac death. The 10-year mortality rate is 50% if untreated. A postpubertal QTc >470 ms for men, >480 ms for women and >460 ms for children should serve as a cutoff for the genetic diagnosis.

GENE PANEL

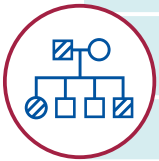
11 genes CACNA1C, CALM1, CALM2, CALM3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, SCN5A, TRDN

Identification of carriers enables therapy and reduces risk of cardiac events

10-year **mortality rate is 50%** if untreated

Pathogenic **variants are detected in ~90-95%** of genetic positive cases

All LQTS patients should modify their lifestyle from the time of diagnosis (e.g., by avoiding drugs that prolong the QTc) and be treated with beta-blockers. The implantation of an ICD is recommended where there is refractory recurrent syncope/ventricular tachycardia, a history of cardiac arrest, or in LQTS2 patients with a QTc>500 ms. Delayed drug metabolism, which can be caused by variants in the *CYP2D6*, *CYP2C9* or *CYP2C19* gene, can enhance the affect of drugs that prolong the QTc. In drug-induced LQTS, supplementary diagnostics of the cytochrome *P450* genes may be useful.



	PREVALENCE	INHERITANCE PATTERN
LQTS type 1	1:2,500	Autosomal dominant and recessive (RW and JLN)
LQTS type 2		Autosomal dominant (RW)
LQTS type 3		Autosomal dominant (RW)

CARDIOMYOPATHIES
ARRYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY PANEL

BACKGROUND

Arrythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease of the heart muscle in which the myocardium is progressively replaced by fatty and connective tissue. About one third of the index patients with ARVC die suddenly between the ages of 14-20 years. However, half of the carriers do not develop clinical symptoms until over 50 years old and about one third do not become ill until old age. More than 10 different forms of ARVC have now been documented.

The connective tissue remodeling of the heart muscle, which mainly affects the right ventricle, disturbs stimulus conduction and leads to ventricular arrythmias, palpitations or syncope. The ECG typically shows epsilon waves and an inverted T-wave with broadened QRS complex in the right precordial lead recording. The arrythmias that can lead to sudden cardiac death are usually triggered by physical exertion.

Our panel includes variants in genes that code for components of the desmosomes (cell-cell connections) which causes most forms of ARVC. Genetic analysis of the *DSP*, *PKP2* and *DSG2* genes reveal pathogenic variants in about 50-60% of patients. Further causes of the hereditary form of ARVC that are found in about 5% of cases are variants of other genes that code for desmosomal proteins, such as *JUP*, *DSC2*, *TMEM43* and *TGFB3*. To date, no genetic cause can be proven in about 40% of ARVC cases.

GENE PANEL

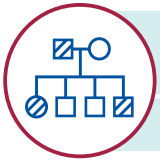
8 genes DSC2, DSG2, DSP, JUP, LMNA, PKP2, TGFB3, TMEM43

Physical exertion can trigger sudden cardiac death

1/3 of index patients die suddenly between 14-20 years old

50% of carriers do not develop symptoms until over 50 years old

ARVC can be difficult to diagnose as the changes in the heart can be subtle and the fat deposits can be hard to see. There is no cure for ARVC, however, treatments are used to reduce and control symptoms, and reduce the risk of complications. Treatment focuses on improving the pumping of the heart, controlling arrythmias and reducing the risk of cardiac arrest. Recommended treatments include beta-blockers, diuretics, antiarrythmic drugs, ACE inhibitors, anticoagulants, catheter ablation and an ICD.



PREVALENCE	INHERITANCE PATTERN
1:5,000	Autosomal dominant

CARDIOMYOPATHIES
DILATED CARDIOMYOPATHY PANEL

BACKGROUND

Dilated cardiomyopathy (DCM) is characterized by dilation and limited contraction of the left or both ventricles and is usually accompanied by progressive heart failure. There is a significantly increased risk of arrythmias, thromboembolism and sudden cardiac death. Although therapy has improved, the 5-year survival rate is 36-80%. Half of the DCM cases with an unclear cause are idiopathic (IDCM) and are not secondary to other primary diseases. Consequently, it is important to rule out secondary DCM before genetic diagnosis is undertaken. In up to 40% of cases, IDCM is genetically determined. The early identification of carriers is essential to positively influence the course of the disease.

The genetic causes of IDCM are heterogeneous and the phenotype also depends on the penetrance and malignancy of the affected gene. Patients with pathogenic *TTN* variants usually show a milder course and respond better to therapy; however, ventricular arrythmias are also more commonly reported in these patients. Patients with pathogenic variants in the *LMNA*, *PLN*, *RBM20*, *FLNC*, *DES* and *SCN5A* genes have an increased risk of a worse prognosis and malignant arrythmias. The phenotype also depends on the penetrance and malignancy of the affected gene.

GENE PANEL

66 genes

ABCC9, ACADVL, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CAV3, CHRM2, CPT2, CRYAB, CSRP3, CTF1, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, EMD, EYA4, FHL2, FLNC, FKRP, FKTN, GATA4, GATA6, GATAD1, ILK, JUP, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEBL, NEXN, NKX2-5, NPPA, PKP2, PLN, PDLIM5, RAF1, RBM20, RYR2, SCN5A, SDHA, SGCD, SLC22A5, TAZ, TCAP, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL

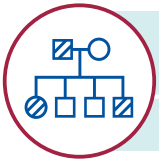
Increased risk of **arrythmias, thromboembolism and sudden cardiac death**

Pathogenic variants **in over 40 genes**

Early identification of carriers positively influences course of the disease

Over 40 pathogenic genes are now known. A large study found that approximately 6-8% of IDCM/FDCM patients carry variants in *LMNA*. About a quarter of all cases carry variants in the genes of the heavy chain of ß-myosin (*MYH7*), myosin binding protein C (*MYBPC3*) and troponin T (*TNNT2*). Although variants in these genes have been described much more frequently in connection with hypertrophic cardiomyopathy, more than 100 different variants specific to DCM are now known. With the analysis of four commonly affected genes, pathogenic variants can be detected in about one third of all IDCM/FDCM cases.

Recent studies in over 300 IDCM patients have shown that variants in the largest human gene titin (*TTN*) are causally related in about 25% of cases. These are severe variants that lead to functional loss. However, the penetrance of these variants is not complete, so that the causation in each family should be verified by the targeted analysis of several family members. Due to its size, this gene can only be analyzed using new sequencing methods. This method also offers the advantage that more than 30 genes in which variants associated with DCM have frequently been identified can be analyzed in parallel.



PREVALENCE	INHERITANCE PATTERN
1:2,500	Autosomal dominant

CARDIOMYOPATHIES
HYPERTROPHIC CARDIOMYOPATHY PANEL

BACKGROUND

Hypertrophic cardiomyopathy (HCM) is a structural disease of the heart muscle. The average life expectancy of those affected is 66 years, with the prognosis depending on the underlying molecular cause. To date, appoximately 2,000 pathogenic variants in over 40 different genes, most of which code for cardiac structural proteins, have been identified in connection with HCM. About 90% of these variants are found in the *MYH7*, *MYBPC3*, *TNNT2* and *TNNI3* genes.

HCM is usually associated with an asymmetric increase in the muscle mass of the left ventricle with involvement of the interventricular septum, resulting in characteristic changes in the ECG (Q wave, ST segment and P wave). The phenotypic manifestation of HCM varies from benign, incompletely penetrating forms to malignant forms with a high risk of sudden cardiac death from childhood onwards.

GENE PANEL

60 genes

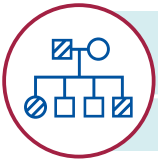
ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ANKRD1, BAG3, BRAF, CACNA1C, CAV3, CALR3, CBL, CHRM2, CPT2, CSRP3, CTF1, DES, ELAC2, FHL1, FHL2, FLNC, GAA, GATA4, GLA, HRAS, JPH2, KRAS, LAMP2, LDB3, MAP2K1, MAP2K2, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEXN, NF1, PLN, PDLIM5, PRKAG2, PTPN11, RAF1, RASA1, SHOC2, SOS1, SPRED1, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL

Patients average **life expectancy is 66 years**

Pathogenic variants **in over 40 genes**

Pathogenic variants detected in **60% of all HCM cases**

Routine diagnostics can currently detect pathogenic variants in approximately 60% of all HCM cases. Deletions of single exons or entire genes are very rare (<1% of all cases) and are also investigated here. Periodic re-evaluation is recommended, including in asymptomatic patients. The majority of patients with HCM are asymptomatic or minimally symptomatic and do not require pharmacological treatment. However, in patients at high risk of SCD, the SCD risk caused by ventricular fibrillation can be reduced with an ICD.



PREVALENCE	INHERITANCE PATTERN
1:500 (Caucasian population)	Autosomal dominant

CARDIOMYOPATHIES
RESTRICTIVE CARDIOMYOPATHY PANEL

BACKGROUND

Restrictive cardiomyopathy (RCM) is a rare cardiomyopathy, characterized by restricted ventricular filling and reduced diastolic volume with normal systolic functioning and normal or nearly normal myocardial thickness. RCM can appear anytime from childhood to adulthood.

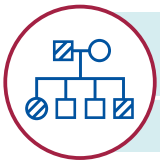
Childhood symptoms include failure to gain weight and grow at the expected rate, fatigue, and fainting. Severe symptoms may include abnormal swelling or puffiness (edema), increased blood pressure, enlarged liver, abnormal buildup of fluid in the abdominal cavity (ascites), and lung congestion. Although some children remain asymptomatic, they may die suddenly due to heart failure. Without treatment, the majority of affected children survive only a few years following diagnosis.

Symptoms in adults include shortness of breath, fatigue, and a reduced ability to exercise. Some individuals have arrythmia and may also experience chest palpitations and dizziness. Abnormal blood clots are common. Without treatment, approximately one-third of adults do not survive for more than five years following a diagnosis.

In a study of ten unrelated RCM patients, *TNNI3* mutations were detected in seven. Several other causative genes have been identified in individual cases, including *TNNT2*, *ACTC1* and *DES*.

GENE PANEL

6 genes DES, FLNC, MYBPC3, MYH7, TNNI3, TNNT2



PREVALENCE	INHERITANCE PATTERN
Unknown, rare	Autosomal dominant

CARDIOMYOPATHIES
LEFT VENTRICULAR/NONCOMPACTION CARDIOMYOPATHY PANEL

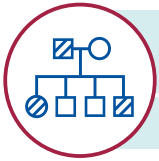
BACKGROUND

Left ventricular/noncompaction cardiomyopathy (LVNC) is a myocardial disorder. LVNC can be a morphological manifestation of several different cardiomyopathies. In pediatric patients, the prevalence of LVNC is up to 9% of all primary cardiomyopathies, making it the third most common cardiomyopathy after DCM and HCM. Our panel includes genes that have been most frequently affected. However, even with extended diagnostics, no relevant variant can be detected in about 60-70% of cases.

LVNC is characterized by protruding ventricular trabeculae and deep indentations of the subendocardial surface of the left and sometimes right ventricle, which extend from the ventricular cavity to the edge of the epicardium and occur with or without left ventricular dysfunction. Common symptoms include breathlessness, swelling of the ankles and fatigue with limited physical capacity and exercise intolerance. The recommended treatment includes ACE inhibitors, beta-blockers, diuretics and blood thinners, and in severe cases a heart transplant is necessary.

GENE PANEL

10 genes ACTC1, CASQ2, HCN4, LDB3, MYBPC3, MYH7, PRDM16, TAZ, TNNT2, TPM1



PREVALENCE	INHERITANCE PATTERN
1:500	Autosomal dominant

CONGENITAL HEART DEFECTS
COMPREHENSIVE PANEL

BACKGROUND

Congenital heart defects (CHD) are observed in approximately eight out of every 1,000 live births and are one of the most common causes of child morbidity and mortality worldwide. They can run in families, in both syndromic and isolated forms. More than 80 genes are known to be associated with isolated and more common syndromic forms of CHD.

It is possible to investigate genetic causes of CHD such as atrial septum defect, ventricular septum defect, tetralogy of Fallot, transposition of the large arteries, hypoplastic left heart syndrome, aortic stenosis, pulmonary stenosis, conotruncal defects, Ebstein anomaly and heterotaxy, as well as RASopathies and other syndromes in familial cases or when an overriding syndrome is suspected.

The causes of CHD are diverse and often multifactorial. It is now assumed that a significant proportion of congenital cardiac malformations are genetic, whereas suspected external factors are still largely unexplained. Our comprehensive panel with 91 genes covers many CHD, including Alagille syndrome, isolated and syndromic CHD, RASopathies and heterotaxy. Additionally, we offer targeted panels for the different types of CHD.

GENE PANEL

91 genes

ACTC1, ACVR2B, ADAMTS10, ARHGAP31, BMPR2, BRAF, CBL, CFAP53, CHD7, CITED2, CREBBP, CRELD1, DNAH11, DNAH5, DNAI1, DOCK6, DTNA, EHMT1, ELN, EOGT, EP300, EVC, EVC2, FBN1, FBN2, FLNA, FOXC1, FOXH1, FOXP1, GATA4, GATA5, GATA6, GDF1, GJA1, GPC3, HRAS, JAG1, KDM6A, KMT2D, KRAS, LEFTY2, LZTR1, MAP2K1, MAP2K2, MED12, MED13L, MGP, MMP21, MRAS, MYH11, MYH6, NF1, NIPBL, NKX2-5, NKX2-6, NODAL, NOTCH1, NOTCH2, NPHP4, NR2F2, NRAS, NSD1, PITX2, PKD1L1, PPP1CB, PTPN11, RAF1, RBM10, RBPJ, RIT1, RRAS, SALL1, SALL4, SEMA3E, SHOC2, SMAD6, SOS1, SOS2, SPRED1, TAB2, TBX1, TBX20, TBX3, TBX5, TFAP2B, TGFBR1, TGFBR2, TLL1, ZEB2, ZFPM2, ZIC3

SYNDROMES INCLUDED

- Adams-Oliver syndrome
- Alagille syndrome
- Char syndrome
- CHARGE syndrome
- Cornelia-de-Lange syndrome
- Costello syndrome
- Ellis-van-Creveld syndrome
- Heterotaxy syndrome
- Holt-Oram syndrome
- Kabuki syndrome
- Keutel syndrome
- Kleefstra syndrome
- Loeys-Dietz syndrome
- Lujan-Fryns syndrome
- Mowat-Wilson syndrome
- Noonan syndrome
- Williams-Beuren syndrome

POSSIBLE SYMPTOMS

- A bluish tint to the skin, lips and nails (cyanosis)
- Shortness of breath
- Rapid breathing and heartbeat
- Swelling of body tissue or organs
- Extreme tiredness and fatigue
- Exercise intolerance and fainting

CHD patients or family members who want to start a family

A child born **with heart defects**

A **child with neurodevelopmental delay** who might have a hereditary heart disorder

CONGENITAL HEART DEFECTS
ALAGILLE SYNDROME PANEL

BACKGROUND

Alagille syndrome is clinically highly variable. However, characteristic facial features are found. The morbidity and mortality are mainly determined by the cardiological and hepatic symptoms. Our panel includes pathogenic variants of two genes that can confirm a clinical diagnosis.

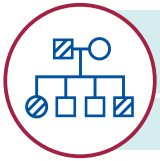
Patients show symptoms in several organ systems, mainly due to intrahepatic bile duct hypoplasia and the resulting cholestasis in the liver. Congenital heart defects, especially pulmonary artery stenosis, as well as vertebral anomalies in the form of butterfly-shaped vertebrae and a posterior embryotoxon in the eye are also seen. A clinical suspected diagnosis is made primarily on the basis of a typical combination of characteristics.

The vast majority of patients carry pathogenic variants in *JAG1*, 5-10% of which are caused by microdeletions of all or part of the gene. Only about 1-2% of patients carry pathogenic variants in *NOTCH2*. Familial occurrence is observed in 30-50% of those affected.

The recommended treatment for Alagille syndrome is ursodeoxycholic acid to increase bile flow.

GENE PANEL

2 genes — JAG1, NOTCH2



PREVALENCE	INHERITANCE PATTERN
1:30,000	Autosomal dominant

CONGENTIAL HEART DEFECTS
RASOPATHIES WITH HEART DEFECTS PANEL

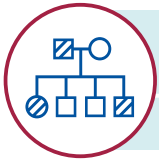
BACKGROUND

RASopathies is the term for a clinically and genetically heterogeneous group of disorders that are caused by germline mutations in genes that encode protein components of the Ras/mitogen-activated-protein kinase (MAPK) pathway. The Ras/MAPK pathway plays an essential role in processes crucial for normal development: regulation of the cell cycle, differentiation, growth and apoptosis. Therefore, dysregulation of this pathway has a profound impact on development. Several of these disorders may be caused by pathogenic changes in various genes of the Ras/MAPK pathway, most of which are activating changes which increase signal transduction within this pathway.

Several organ systems, including the cardiovascular system, are affected. The syndromes overlap significantly in their signs and symptoms, which may complicate establishing a clear diagnosis and targeted diagnostic procedures.

GENE PANEL

16 genes BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, MRAS, NRAS, PPP1CB, PTPN11, RAF1, RIT1, SHOC2, SOS1, SOS2



PREVALENCE	INHERITANCE PATTERN
1:1,000	Autosomal dominant

SYNDROMIC CONGENITAL HEART DEFECTS PANEL

The molecular basis of many CHD syndromes has been identified. Monogenic syndromes can include, among others, Holt-Oram, Char, Ellis-van Creveld, Adams-Oliver and Kabuki syndrome.

Holt-Oram syndrome is an autosomal dominant disorder most commonly involving an atrial or ventricular septal defect (ASD or VSD). Overall, 70% of cases are caused by a heterozygous pathogenic variant in *TBX5*. Char syndrome is autosomal dominantly inherited with patent ductus arteriosus (PDA) as the primary cardiac finding, but other heart defects, such as VSD, have also been reported. Approximately ~50% of families with a clinical diagnosis of Char syndrome have a heterozygous pathogenic variant in *TFAP2B*. Ellis-van Creveld syndrome is an autosomal recessive skeletal dysplasia associated with a primary ASD resulting in a common atrium. Two-thirds of cases of Ellis-van Creveld syndrome are caused by homozygous or compound heterozygous variants in the *EVC* or *EVC2* genes. Adams-Oliver syndrome can be inherited autosomal dominantly or recessively. Malformations can include heart, scalp and limbs. Pathogenic variants in *ARHGAP31*, *DOCK6*, *RBPJ*, *EOGT*, *NOTCH1* and *DLL4* have been reported. Kabuki syndrome (KS) has both X-linked and autosomal dominant pathogeneses. CHD occur in 40% to 70% of individuals with KS. The most common cardiac malformations are coarctation of the aorta, ASD, and VSD. KS is mainly caused by pathogenic variants in the *KMT2D* and *KDM6A* genes.

37 genes

ADAMTS10, ARHGAP31, CHD7, CREBBP, DOCK6, EHMT1, EOGT, EP300, EVC, EVC2, FBN1, FBN2, FLNA, FOXC1, GPC3, JAG1, KDM6A, KMT2D, MED12, MGP, MYH11, NIPBL, NOTCH1, NOTCH2, NSD1, PITX2, RBM10, RBPJ, SALL1, SALL4, SEMA3E, TBX3, TBX5, TFAP2B, TGFBR1, TGFBR2, ZEB2

ISOLATED CONGENITAL HEART DEFECTS PANEL

Isolated CHD are caused by variants in genes encoding transcription factors, signaling molecules, or structural proteins important in cardiac development, structure and function. Most cases of isolated CHD occur sporadically without a strong family history. Cardiac malformations can include atrial septal defects, tetralogy of Fallot, and left-sided lesions. Between 5–10% of sporadic isolated CHD can be due to a copy number variant (CNV). Some CNVs have been mapped to chromosomal regions previously known to contain genes pathogenetically related to CHD.

22 genes

ACTC1, BMPR2, CITED2, DTNA, ELN, FOXH1, FOXP1, GATA4, GATA5, GATA6, GJA1, MED13L, MYH6, NKX2-5, NKX2-6, NR2F2, SMAD6, TAB2, TBX1, TBX20, TLL1, ZFPM2

HETEROTAXY PANEL

Heterotaxy is associated with CHD in 50% to 95% of cases, and includes cardiac findings such as atrioventricular canal defects that are frequently unbalanced. It is estimated to occur in 1 in 10,000 live births and constitutes approximately 3% of CHD cases. Heterotaxy has the highest relative risk among all classes of CHD, which supports a strong genetic component. Clinically relevant CNV have been identified in 15% to 26% of patients with heterotaxy syndrome. Autosomal dominant, autosomal recessive, and X-linked inheritance patterns have all been described, but unlike other types of CHD, *de novo* variants are not major contributors to heterotaxy. The hallmark of CHD in heterotaxy is that there is no absolutely defined pattern to the possible combinations of cardiac and vascular defects.

5 genes

CRELD1, DNAI1, DNAH5, DNAH11, GDF1

AORTIC DISORDERS
COMPREHENSIVE PANEL

BACKGROUND

Aortic diseases are congenital, genetically determined disorders of a) the extracellular matrix proteins, b) the TGF-beta signal transduction pathway or c) the structural proteins of the smooth vascular muscles. While disorders under a) and b) lead to a weakening of the connective tissue structure of the vascular adventitia, malfunctions under c) are associated with loss of contractile function. Both are associated with an increased risk of aneurysms (ruptures) in the arterial system. Serious, life-threatening complications range from ruptures of the ascending aorta to mesenteric artery rupture (e.g., during pregnancy). Aortic diseases show genetic and phenotypic heterogeneity and are characterized by pleiotropy. Numerous, clinically definable differential diagnoses have been reported and genetically characterized. We offer a comprehensive panel with 37 genes covering several aortic disorders.

Additionally, we offer targeted panels for Ehlers-Danlos syndrome, Marfan syndrome and Marfan-like disorders.

GENE PANEL

37 genes

ACTA2, BGN, CBS, COL1A1, COL3A1, COL4A5, COL5A1, COL5A2, EFEMP2, ELN EMILIN1, FBLN5, FBN1, FBN2, FLNA, FOXE3, GATA5, LOX, LTBP3, MAT2A, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, ROBO4, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1, TGFBR2

SYNDROMES INCLUDED

- Bicuspid aortic valve
- Cutis laxa
- Ehlers-Danlos syndrome
- Loeys-Dietz syndrome (type 1-6)
- Marfan syndrome
- Thoracic aortic aneurysms and aortic dissections

POSSIBLE SYMPTOMS

- Pain in the jaw, neck, chest, or back
- Swelling in the arms, neck, or head
- Difficult or painful swallowing
- Shortness of breath
- Numbness or tingling (paresthesias)
- Tall stature
- Long slender fingers
- Pale, fragile, easily bruised skin
- Joint hypermobility
- Sunken or protruding chest

TARGET POPULATION

People with a **family history** of unexplained cardiac arrest, cardiac death or sudden aortic events

People with a clinical diagnosis of an aortic disorder who **need a differential diagnosis**

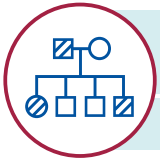
Patients who need prophylactic aortic surgery and want to **determine the right timing**

Patients with a hereditary heart disorder who want to estimate **the risk of a pregnancy**

THORACIC AORTIC ANEURYSMS AND AORTIC DISSECTIONS

Thoracic aortic aneurysms and dissections (TAAD) may occur due to a genetically determined syndrome or in isolation. About 10-20% are inherited in an autosomal dominant manner with reduced penetrance and variable expression. TAAD are clinically and genetically heterogeneous. Mutations in several genes are associated with familial TAAD. Mutations in the *ACTA2* gene have been identified in 14-20% of TAAD cases, mutations in the *TGFBR2* gene have been found in 2.5% of cases, and mutations in both *TGFBR1* and *TGFBR2* account for 5% of TAAD cases.

Aortic aneurysms usually have no symptoms. However, depending on the size, growth rate and location of these abnormalities, they can cause pain in the jaw, neck, chest, or back; swelling in the arms, neck, or head; difficult or painful swallowing; hoarseness; shortness of breath; wheezing; a chronic cough; or coughing up blood. Aortic dissections usually cause severe, sudden chest or back pain. They may also result in unusually pale skin, a very faint pulse, numbness or tingling in one or more limbs, or paralysis.



PREVALENCE	INHERITANCE PATTERN
1:5,000	Autosomal dominant

LOEYS-DIETZ SYNDROME

Loeys-Dietz syndrome (LDS) is characterized by vascular involvement (with cerebral, thoracic and abdominal arterial aneurysms and dissections), skeletal involvement (scoliosis, joint hypermobilty, arachnodactyly, talipes equinovarus and spinal instabilities), craniofacial involvement (widely spaced eyes, strabismus, split uvula or cleft palate and craniosynostosis) and skin involvement (velvety and translucent skin, easy bruising and dystrophic scars).

There are five types of LSD: LDS1 (*TGFBR1* variants), LDS2 (*TGFBR2* variants), LDS3 (*SMAD3* variants), LDS4 (*TGFB2* variants), LDS5 (*TGFB3* variants) and LDS6 (*SMAD2* variants). Severity of the disease depends on which gene is altered: LDS1=LDS2>LDS3>LDS4>LDS5.

Clinical diagnosis of LDS can be made if a pathogenic variant in one of the above-mentioned genes is detected and is present in combination with aortic root enlargement (z-score >2.0) or a type A dissection, or if there is additional systemic involvement with characteristic craniofacial, vascular, skeletal or skin manifestations.

To date, variants in the *TGFBR2* gene have been identified in 55-60% of LDS patients, variants in the *TGFBR1* gene in 20-25%, variants in the *SMAD3* or *TGFB2* genes in 5-10%, and in the *TGFB3* or *SMAD2* genes in 1-5%. The detection rate of *TGFBR1/2* variants in patients with LDS1 and LDS2 is 95%.

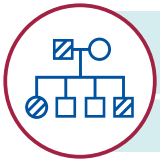
Patients with *TGFBR1* or *TGFBR2* variants are not clinically distinguishable. Patients with *SMAD3* variants have a higher risk of osteoarthritis. Patients with *TGFB2* variants are usually large, often have mitral valve insufficiency, and overall have many overlaps with Marfan syndrome. Patients with *TGFB3* variants show additional clinical overlaps with Shprintzen-Goldberg syndrome and Loeys-Dietz syndrome with cardiovascular involvement.

BICUSPID AORTIC VALVE

A bicuspid aortic valve (BAV) is a common heart malformation. Many patients with a BAV have a positive family history and can develop further complications such as aortic insufficiency, aortic stenosis, and aortic aneurysms and dissections. The genetic etiology of BAV is heterogeneous. Sometimes a BAV occurs in connection with a syndromic aortic disease such as Loeys-Dietz syndrome or non-syndromic familial thoracic aortic aneurysms and dissections.

Pathogenic variants have been identified in multiple genes, including *NOTCH1* (up to 10% of families with BAV), *SMAD6* (1-3% of patients with BAV and aortic dissections), *ROBO4* (2% of patients with BAV and ascending aortic aneurysms ± atrial septal defect) and *GATA5* (1-3% of patients with BAV).

Children and adults with a BAV require regular monitoring in order to detect any changes in their condition, such as aortic valve stenosis, aortic valve regurgitation or an enlarged aorta. Early detection can help with eventual treatment.

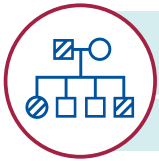


PREVALENCE	INHERITANCE PATTERN
0.2 to 2% (general population)	Autosomal dominant

CUTIS LAXA

Cutis laxa is a rare, genetically heterogeneous, generalized disease of the connective tissue that is characterized by loose, wrinkled skin. In contrast to hyperelastic skin, there seems to be excess skin which is inelastic. In addition, skeletal and developmental anomalies, and in some cases severe systemic involvement are described. Histopathology shows diminished, fragmented elastic fibers. In the dominant forms, skin laxity manifests rather late, while in the recessive forms, skin involvement is seen earlier. Mild visceral involvement may include emphysema, bronchiectasis, pulmonary stenosis and intestinal hernias. In some cases, intrauterine growth retardation is noticeable. Facial abnormalities and chest and spinal deformities are common. Lung involvement with the early onset of emphysema and pneumothoraces, vascular involvement, as well as hernias and diverticula in the digestive and urogenital areas influence the severity.

Cutis laxa is inherited in different ways, depending on the type. There are autosomal dominant and autosomal recessive forms of inherited cutis laxa. The usually mild autosomal dominant form is caused by pathogenic variants in the *ADCL1*, *ADCL2* and *ADCL3* genes. Whereas, the severe autosomal recessive form is caused by pathogenic variants in the *ARCL1A*, *ARCL1B*, *ARCL1C*, *ARCL2A*, *ARCL2B*, *ARCL2C*, *ARCL2D*, *ARCL3A* and *ARCL3B* genes. Both forms are genetically heterogeneous and clinically difficult to differentiate.



PREVALENCE	INHERITANCE PATTERN
200 families reported	Autosomal dominant

BACKGROUND

Ehlers-Danlos syndrome (EDS) refers to a clinically and genetically heterogeneous group of connective tissue disorders characterized by joint hypermobility, highly elastic (stretchy) skin, and tissue fragility. The revised international classification of 2017 proposes 13 subtypes based on clinical criteria, which are inherited in an autosomal dominant or recessive manner and, with the exception of the hypermobile EDS subtype, can be confirmed by genetic data.

Autosomal dominant subtypes include arthrochalasia EDS (aEDS), classical EDS (cEDS), periodontal EDS (pEDS) and vascular EDS (vEDS). Autosomal recessive subtypes include Brittle cornea syndrome (BCS), cardiac-valvular EDS (cvEDS), classical-like (clEDS), dermatosparaxis EDS (dEDS), kyphoscoliotic EDS (kEDS), musculocontractural EDS (mcEDS) and spondylodysplastic EDS (spEDS). Myopathic EDS (mEDS) can be inherited in an autosomal dominant or recessive manner.

The individual EDS subtypes are caused by different gene variants resulting in defects in collagen biosynthesis and processing, collagen folding, the structure and function of the interface between muscle and the extracellular matrix, glycosaminoglycan biosynthesis, the complement pathway, and intracellular processes. A clinical differentiation of EDS subtypes is often difficult as they can overlap with other connective tissue diseases. A genetic diagnosis can support the differentiation.

GENE PANEL

29 genes

ADAMTS2, AEBP1, B3GALT6, B4GALT7, C1R, C1S, CHST14, COL12A1, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, DSE, EMILIN1, FKBP14, FLNA, PHYKPL, PIEZO2, PLOD1, PLOD3, PRDM5, SLC2A10, SLC39A13, TNXB, ZNF469

	PREVALENCE	INHERITANCE PATTERN
Arthrochalasia	Unknown	Autosomal dominant
Classical	1 in 20,000	
Periodontal	Unknown	
Vascular	1 in 50,000	
Brittle cornea syndrome	<1 in 1,000,000	Autosomal recessive
Cardiac-valvular		
Classical-like		
Dermatosparaxis		
Kyphoscoliotic	Unknown	
Musculocontractural	<1 in 1,000,000	
Spondylodysplastic		
Myopathic	<1 in 1,000,000	Autosomal dominant or recessive

AORTIC DISORDERS
MARFAN SYNDROME PANEL

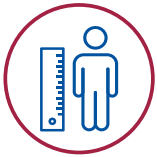
BACKGROUND

Classic Marfan syndrome (MFS) is the most common connective tissue disorder. It is caused by pathogenic variants in the *FBN1* gene, which codes for fibrillin-1. Fibrillin is secreted by fibroblasts and is, together with collagen and elastin, the most important structural component of the extracellular connective tissue matrix. Pathogenic variants in *FBN1* can lead to a broad spectrum of clinical manifestations in different organ system.

The clinical symptoms predominantly involve the cardiovascular system, skeleton and the eyes (lens dislocation or ectopia lentis). A diagnosis of MFS can be confirmed when isolated aortic root dilatation/dissection is present and a pathogenic variant in the *FBN1* gene detected, or when isolated ectopia lentis combined with the detection of a pathogenic variant in the *FBN1* gene is described in connection with aortic root dilatation. In the presence of aortic root dilatation (z-score >2) and negative *FBN1* analysis, examination of the *TGFBR1* and *TGFBR2* genes is recommended.

GENE PANEL

3 genes — FBN1, TGFBR1, TGFBR2



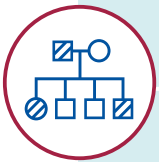
Patients have tall, slender build with long limbs

Patients have sunken or protruding chest

50% of patients show lens dislocation

In patients with classic Marfan syndrome, pathogenic variants in the *FBN1* gene are identified in up to 95% of cases. In 5-25% of patients who show partial symptoms of MFS with additional features (patients with Marfan-like syndrome or incomplete Marfan symptoms) and in whom no pathogenic variant in the *FBN1* gene can be detected, variants in *TGFBR1* and *TGFBR2* have been identified. The mutation detection rate in *TGFBR1* and *TGFBR2* in thoracic aortic aneurysms and dissections is about 5%.

While MFS has no cure, treatments can help managing the symptoms and reducing the risk of complications, especially when started early. The type of treatment depends on the affected body parts and the severity of the condition. Medication to lower blood pressure is recommended to help prevent the aorta from enlarging and to reduce the risk of dissection and rupture. Beta-blockers or angiotensin receptor blockers (ARBs) are most commonly prescribed. Calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors may be prescribed if side effects from beta blockers or ARBs occur.



PREVALENCE	INHERITANCE PATTERN
1:5,000	Autosomal dominant (mild) or recessive (severe)

BACKGROUND

Ectopia lentis is caused by heterozygous *FBN1* variants and characterized by a lens luxation that is not associated with aortic root dilatation. Ectopia lentis is caused by homozygous or combined heterozygous *ADAMTS4* variants and characterized by an autosomal recessively inherited isolated lens dislocation.

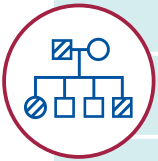
MASS phenotype is also caused by pathogenic *FBN1* variants. Symptoms include myopia, mitral valve prolapse, borderline aortic root dilatation, striae and skeletal involvement. Pathogenic *SKI* variants are causal for Shprintzen-Goldberg syndrome. Due to the phenotypic overlap of craniofacial, cardiovascular, skeletal and skin manifestations, it is a differential diagnosis for Loeys-Dietz and Marfan syndromes. Additional symptoms can involve mental retardation, skeletal muscle hypotension and marfanoid habitus.

Congenital contractural arachnodactyly is caused by pathogenic *FBN2* variants. Symptoms include marfanoid habitus, arachnodactyly, joint contractures, kyphoscoliosis, muscle hypotonia, auricular dysplasia and aortic root enlargement. Lujan-Fryns syndrome or X-linked mental retardation with marfanoid habitus is inherited in a X-linked recessive pattern with pathogenic variants in *MED12*, *UPF3B* and *ZDHHC9*. Symptoms include marfanoid habitus, craniofacial features, generalized muscle hypotension and behavioral problems.

Weill-Marchesani syndrome (WMS) is caused by pathogenic homozygous or combined hetrozygous variants in the *ADAMTS10* gene in most patients. Pathogenic variants in the *LTBP2*, *ADAMTS17*, *ADAMTS17* and *FBN1* genes also cause WMS. Symptoms include characteristic eye problems (microspherophakia, severe myopia, ectopia lentis and glaucoma) as well as short stature, brachydactyly, joint stiffness, and cardiac abnormalities (pulmonary valve stenosis, mitral regurgitation and aortic valve stenosis).

GENE PANEL

12 genes ADAMTS10, ADAMTS17, ADAMTSL2, ADAMTSL4, FBN1, FBN2, LTBP2, LTBP3, MED12, SKI, UPF3B, ZDHHC9



	PREVALENCE	INHERITANCE PATTERN
Congenital contractural arachnodactyly	1:10,000	Autosomal dominant
Ectopia lentis and Ectopia lentis 2	<1:1,000,000	Autosomal dominant or recessive
Lujan-Fryns syndrome	Unknown	X-linked recessive
MASS phenotype	2.4% (general population)	X-linked or autosomal dominant
Shprintzen-Goldberg syndrome	Unknown	Autosomal dominant
Weill-Marchesani syndrome	1:100,000	Autosomal dominant or recessive

MEDICOVER
GENETICS

www.medicover-genetics.com