

Noonan syndrome

- Autosomal dominant disorder affecting between 1/1,000 and 1/2,500 people
- Associated with short stature, developmental delay and congenital heart defects
- 20%-30% of individuals have congenital or childhood-onset HCM
- Management includes treatment of cardiovascular anomalies, early intervention of developmental disabilities and growth hormone treatment when appropriate
- A genetic mutation is identified in up to 85% of affected individuals
- **Genetic diagnosis of Noonan syndrome facilitates appropriate screening, intervention and treatment of associated health issues**

Marfan syndrome

- Autosomal dominant connective tissue disorder that affects 1 in 5,000 people and is associated with cardiovascular, skeletal and ocular findings
- Associated with an increased risk for thoracic aortic aneurysms (TAA) and a greater risk for dissection than other non-genetic forms of TAA and thus surgical intervention is recommended at lower thresholds
- A genetic mutation is identified in 95% of individuals with a clinical diagnosis
- **Genetic testing has significant treatment and family screening implications**

Loeys-Dietz syndrome

- Rare autosomal dominant connective tissue disorder associated with skeletal, cutaneous, and cardiovascular findings
- Reduced life expectancy due to a high risk of aggressive cerebral, thoracic and abdominal aneurysms
- Screening by MRA or CTA of full arterial tree is recommended
- Similar skeletal features as Marfan syndrome
- High risk of aortic dissection at small diameters leading to limited life expectancy
- Threshold for surgical intervention is lower than Marfan syndrome
- Genetic mutation identified in more than 95% of affected individuals
- **Genetic testing has significant treatment and family screening implications**

The 2014 Canadian Cardiovascular Society Position Statement on the management of thoracic aortic disease recommends genetic testing for all patients with suspected Marfan syndrome or Loeys-Dietz syndrome to clarify the nature of the disease and improve clinical and genetic counselling. Genetic counselling and testing should also be offered to first-degree relatives of mutation positive Loeys-Dietz syndrome patients. Genetic testing of first degree relatives of a patient with mutation-positive Marfan syndrome is recommended if a clinical diagnosis is uncertain.

Panels	Genes
Dilated Cardiomyopathy	ABCC9, ACTC1, ACTN2, BAG3, CSRP3, DES, DMD, DSG2, EYA4, FKTN, GATAD1, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, NEXN, PLN, PSEN1, MT-ND1, MT-ND5, MT-ND6, MT-TD, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2, MT-TM, MT-TQ, MT-TS1, MT-TS2, PSEN2, RBM20, SCN5A, SDHA, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL
Hypertrophic Cardiomyopathy	ACTC1, CALR3, CAV3, CSRP3, GLA, JPH2, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZZ2, NEXN, PLN, PRKAG2, SLC25A4, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL
Hereditary Arrhythmia	AKAP9, ANK2, CACNA1C, CACNB2, CASQ2, CAV3, DSC2, DSG2, DSP, GPD1L, JUP, KCNA5, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNQ1, NPPA, PKP2, PLN, RYR2, SCN1B, SCN3B, SCN4B, SCN5A, SNTA1, TGFB3, TMEM43

Panels	Genes	
Hereditary Thoracic Aortic Aneurysm*	MYH11, ACTA2, TGFBRI, TGFB2, FBN1, COL3A1, SMAD3, CBS, FBN2, SLC2A10, MYLK, TGFB2, TGFB3	
Single Gene Tests	Gene(s)	
Fabry disease	GLA	
Loeys-Dietz Syndrome (LDS)	LDS Type 1B	TGFB2
	LDS Type 1B	SMAD3
Marfan Syndrome	FBN1, TGFBRI, TGFB2	
Noonan Syndrome	PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, RIT1	

* Includes Marfan syndrome genes and Loeys-Dietz syndrome genes for LDS Type 1A, 2A, 2B and 4

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RESOURCES

- American Heart Association:** www.heart.org
- Canadian Association of Genetic Counsellors:** www.cagc-accg.ca
- Heart and Stroke Foundation:** www.heartandstroke.com
- The Canadian SADS Foundation:** www.sads.ca



**The Field Of Genetics Is Always Evolving And So Are We
Please Visit Our Website For A Current Test List**



Heart disease affects an estimated 1.4 million Canadians and is one of the leading causes of death in Canada, claiming more than 33,000 lives a year. This large group of diseases includes atherosclerosis, cardiomyopathy, cardiac arrhythmia, thoracic aortic aneurysms, and congenital heart defects. Many of these disorders can be inherited.

WHAT YOU NEED TO KNOW

Inherited heart conditions can affect people of all ages and may be life threatening. Identifying these chronic disorders early can lead to better care and improved outcome. The management of patients with inherited heart disease is complex and requires careful consideration of other family members who may be at increased risk for potentially fatal events.

LifeLabs Genetics offers a variety of multigene panels and single gene tests for hereditary cardiovascular disorders including cardiomyopathies, arrhythmias, thoracic aortic aneurysms, and genetic syndromes associated with cardiovascular disease.

Genetic testing can:

- Establish or confirm a diagnosis
- Provide prognostic information
- Facilitate prevention strategies and direct treatment
- Identify asymptomatic relatives who may be at risk

33,000

The number of lives Heart disease claims per year.

CARDIOMYOPATHY

Cardiomyopathies are progressive chronic diseases of the heart muscle that can lead to arrhythmias and heart failure. They are a leading cause of sudden cardiac death in the young. Signs and symptoms can include chest pain, cough, syncope, dyspnea, fatigue, palpitations, and swelling of the ankles and feet. However, patients are often asymptomatic, even prior to a fatal event. Most forms of cardiomyopathy have a genetic basis. As a result, family members of a patient are often at risk for disease.

More than 50 genes, mostly autosomal dominant, have been implicated with cardiomyopathy.

Most inherited cardiac disorders demonstrate variable disease expression and reduced penetrance, that is, not all mutation positive family members develop disease. Therefore, many affected individuals will not have an obvious family history of cardiac disease. Genetic testing can confirm a suspected clinical diagnosis and facilitate genetic screening of at-risk relatives.

Hypertrophic cardiomyopathy (HCM)

- Affects 1 in 500 people and is the most common cause of sudden cardiac death in the young (age of onset typically ranges from childhood to early adulthood)
- Individuals are often asymptomatic prior to sudden death
- Genetic mutations are identified in 60%-70% of patients with a positive family history of cardiomyopathy and/or sudden cardiac death, and 10%-50% of sporadic cases
- Some mutations are associated with early-onset, rapidly progressive disease and a high risk of sudden death; others are associated with a mild or benign clinical course
- Echocardiographic evidence of hypertrophy is absent in some gene carriers
- Most patients do well with appropriate treatment
- **Genetic testing may predict severity and guide management**

Dilated cardiomyopathy (DCM)

- Affects at least 1 in 2,500 people of all ages
- Leading cause of heart failure and arrhythmia
- Individuals are often asymptomatic in early stages of disease
- 20%-35% of all DCM is familial
- Genetic mutations are identified in 40%-50% of familial cases
- May be associated with skeletal myopathy and conduction defects
- Some genes and mutations are associated with a higher risk of sudden cardiac death
- **Early genetic diagnosis and early treatment may improve prognosis**

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

- Affects 1/1,000 to 1/5,000 individuals and is associated with ventricular arrhythmia and sudden cardiac death in people under 35
- Onset is usually in late teens or early adulthood
- Clinical diagnosis is challenging (there is no single simple diagnostic test)
- 30%- 50% of patients have a positive family history
- Genetic mutations are identified in about 50% of patients with ARVC
- Not all mutation-positive individuals develop disease
- **Genetic testing can confirm a clinically suspected diagnosis**

2011 Canadian Cardiovascular Society and Canadian Heart Rhythm Society joint guidelines recommend genetic testing of all individuals with clinically suspected ARVC, clinically diagnosed HCM, clinically diagnosed familial DCM, and clinically diagnosed ARVC is recommended to facilitate genetic screening of at-risk family members. Finally, cascade genetic testing is recommended for all first-degree relatives of individuals in whom an inherited cardiomyopathy disease-associated mutation has been identified.

ARRHYTHMIA

Cardiac arrhythmias are heart rhythm disorders that can lead to sudden cardiac death. Inherited arrhythmias are caused by abnormal electrical activity of the heart that results in irregular heart beats or an abnormal heart rhythm. As many as 1 in 500 people may have an inherited arrhythmia. Long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome are three important inherited heart rhythm disorders.

Signs and symptoms of inherited arrhythmias include heart palpitations, lightheadedness, chest pain, and syncope or seizures. Many affected individuals are asymptomatic prior to sudden cardiac death. A family history of arrhythmias and/or unexpected sudden death may be present.

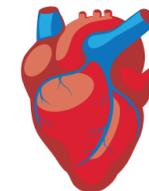
The clinical diagnosis of these disorders can be challenging as electrocardiogram abnormalities may be transient, absent or ambiguous. Genetic testing has become a routine part of clinical care both for accurate diagnosis, and efficient family screening. A correct and early diagnosis is essential so that appropriate preventive measures and treatments that minimize the risk of adverse events can be initiated.

Long QT syndrome (LQTS)

- Affects 1 in 2,000 people of all ages and is associated with sudden cardiac death
- Arrhythmias occur during sleep, or are triggered by exercise, emotional stress, unexpected noise
- Most LQTS is inherited and a genetic mutation is detected in up to 75% of all cases
- Mutation-specific associations predict risk of cardiac events and medication response
- Correct diagnosis and appropriate therapy prevents most deaths
- **Genetic testing is recommended for all individuals with a clinical diagnosis of LQTS as genotyping has diagnostic, prognostic and therapeutic implications**

1.4 million

Canadians are affected by Heart disease each year and it's one of the leading causes of death.



Brugada syndrome

- Rare arrhythmia occurring in 1 in 2,000 individuals and characterized by syncope and sudden death (usually during sleep or at rest)
- 20%-50% of cases are familial
- Clinically variable, onset is usually in adulthood
- Arrhythmia provoked by fever and sodium channel blocking medications
- Mutation detected in up to 40% of all patients with Brugada syndrome
- Not all individuals with a mutation will develop disease
- **Genetic testing is recommended for family screening purposes as prophylactic measures can be taken (minimize risk of fever and avoid certain medications)**

2011 Canadian Cardiovascular Society and Canadian Heart Rhythm Society joint guidelines recommend genetic testing of all individuals with clinically suspected LQTS to assist with diagnosis. In addition, genetic testing of all individuals with clinically diagnosed LQTS is recommended for prognosis, therapeutic decisions, and to facilitate genetic screening of at-risk family members. Genetic testing of symptomatic and asymptomatic individuals with a clinical diagnosis of Brugada syndrome, and all individuals with clinically suspected CPVT is recommended for family screening purposes. Finally, cascade genetic testing is recommended for all first-degree relatives of individuals in whom a disease-associated inherited arrhythmia mutation has been identified.

THORACIC AORTIC ANEURYSM

Only 10% of all aortic aneurysms occur in the thoracic aorta. Most thoracic aneurysms are asymptomatic until a sudden and catastrophic event, or are discovered incidentally during imaging studies. Acute symptoms that suggest aortic dissection include sudden-onset severe chest or back pain, and shortness of breath. Aortic dissection or rupture is associated with life threatening bleeding and shock. Dissection can be avoided by taking appropriate medication and surgically replacing a dilated aorta before it tears. With proper management, life expectancy of an affected individual can be close to normal.

Familial thoracic aortic aneurysms and dissections (FTAAD)

- Up to 20% of individuals with a thoracic aortic aneurysm have a similarly affected first degree relative
- Familial aneurysms typically occur at a younger age, progress more rapidly, and are associated with a higher risk for dissection or rupture than non-genetic aneurysms
- Prophylactic surgical intervention is often recommended at a lower aortic dilation size threshold than for non-genetic forms
- A genetic mutation is identified in 30%-40% of patients with FTAAD
- **Genetic testing has diagnostic, prognostic, and therapeutic implications**
- **Genetic testing can identify relatives who require medical surveillance and possible prophylactic treatment**

The 2014 Canadian Cardiovascular Society Position Statement on the management of thoracic aortic disease recommends genetic testing for all patients with suspected familial aortic aneurysms to clarify the origin of disease and improve clinical and genetic counselling. Genetic counselling and testing should also be offered to first-degree relatives of mutation positive patients.

GENETIC CARDIAC SYNDROMES

Fabry disease

- Rare progressive X-linked metabolic disorder associated with cutaneous, renal, cardiac and neurological abnormalities
- Patients may present with hypertrophic cardiomyopathy (HCM)
- Affected males often develop severe heart and neurological disease; affected females may only have HCM
- 6% of all males diagnosed with HCM at age 40 have Fabry disease
- Enzyme replacement therapy can reduce symptoms and reverse disease progression
- A genetic mutation is identified in more than 99% of patients
- **Genetic diagnosis is critical as it has specific treatment implications**
- **If untreated, Fabry disease impairs the quality of life of the patient and significantly reduces life expectancy**